

(19) World Intellectual Property Organization  
International Bureau



(43) International Publication Date  
25 January 2001 (25.01.2001)

PCT

(10) International Publication Number  
**WO 01/05970 A2**

(51) International Patent Classification<sup>7</sup>: C12N 15/12,  
C07K 14/47, G01N 33/53, C12Q 1/68, A61K 38/17,  
C07K 16/18, A01K 67/027

(21) International Application Number: PCT/US00/19698

(22) International Filing Date: 19 July 2000 (19.07.2000)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:  
60/144,595 19 July 1999 (19.07.1999) US  
60/150,460 23 August 1999 (23.08.1999) US  
60/159,849 15 October 1999 (15.10.1999) US

(63) Related by continuation (CON) or continuation-in-part  
(CIP) to earlier applications:

US 60/144,595 (CIP)  
Filed on 19 July 1999 (19.07.1999)  
US 60/150,460 (CIP)  
Filed on 23 August 1999 (23.08.1999)  
US 60/159,849 (CIP)  
Filed on 15 October 1999 (15.10.1999)

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(81) Designated States (national): AE, AL, AM, AT, AU, AZ,  
BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK,  
DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL,  
IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU,  
LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT,  
RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA,  
UG, US, UZ, VN, YU, ZA, ZW.

(84) Designated States (regional): ARIPO patent (GH, GM,  
KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian  
patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European  
patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE,  
IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG,  
CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

**Published:**

— Without international search report and to be republished  
upon receipt of that report.

For two-letter codes and other abbreviations, refer to the "Guid-  
ance Notes on Codes and Abbreviations" appearing at the begin-  
ning of each regular issue of the PCT Gazette.

(54) Title: GTP-BINDING ASSOCIATED PROTEINS

(57) Abstract: The invention provides human GTP-binding associated proteins (GBAP) and polynucleotides which identify and encode GBAP. The invention also provides expression vectors, host cells, antibodies, agonists, and antagonists. The invention also provides methods for diagnosing, treating, or preventing disorders associated with expression of GBAP.

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## GTP-BINDING ASSOCIATED PROTEINS

### TECHNICAL FIELD

5 This invention relates to nucleic acid and amino acid sequences of GTP-binding associated proteins and to the use of these sequences in the diagnosis, treatment, and prevention of immune system, reproductive, nervous system, and cell signaling disorders, and cell proliferative disorders including cancer.

### 10 BACKGROUND OF THE INVENTION

Guanine nucleotide binding proteins (GTP-binding proteins) are present in all eukaryotic cells and function in processes including metabolism, cellular growth, differentiation, signal transduction, cytoskeletal organization, and intracellular vesicle transport and secretion. In higher organisms they are involved in signaling that regulates such processes as the immune response (Aussel, C. et al. (1988) J. Immunol. 140:215-220), apoptosis, differentiation, and cell proliferation including oncogenesis (Dhanasekaran, N. et al. (1998) Oncogene 17:1383-1394).

The superfamily of GTP-binding proteins can be subdivided into groups such as translational factors, heterotrimeric GTP-binding proteins involved in transmembrane signaling processes (also called G-proteins), proto-oncogene Ras proteins, other low molecular weight GTP-binding proteins including the products of rab, rap, rho, rac, smg21, smg25, YPT, SEC4, and ARF genes, and tubulins (Kaziro, Y. et al. (1991) Annu. Rev. Biochem. 60:349-400).

GTP-binding proteins are involved in protein biosynthesis and include initiation factor 2 (IF-2), elongation factor 2 (EF-Tu), and elongation factor G (EF-G), observed in prokaryotes; and initiation factor 2 (eIF-2), elongation factor 1 $\alpha$  (EF-1 $\alpha$ ), elongation factor 2 (EF-2), and release factor 3 (eRF3) observed in eukaryotes (Kaziro, supra). IF-2 promotes the GTP-dependent binding of the tRNA to the small subunit of the ribosome, the step that initiates protein translation. Elongation factors promote the binding of tRNA and GTP and the displacement of GDP after hydrolysis as protein biosynthesis proceeds. eRF3 participates in the recognition of stop codons and the release of nascent proteins from ribosomes.

30 Heterotrimeric GTP-binding proteins are composed of 3 subunits ( $\alpha$ ,  $\beta$  and  $\gamma$ ) which, in the resting state, associate as a trimer at the inner face of the plasma membrane. Heterotrimeric G-proteins may be classified based on the sequence similarity of  $\alpha$  subunits into the Gs, Gi, Gq and G12 subgroups. In the resting state, the  $\alpha$  subunit binds guanosine diphosphate (GDP), and stimulation of the G-protein by an activated receptor leads to exchange of GDP for guanosine triphosphate (GTP). This exchange results in the separation of the  $\alpha$  from the  $\beta$  and  $\gamma$  subunits, which remain tightly



associated as a dimer. Both the  $\alpha$  subunit and  $\beta$ - $\gamma$  dimer are then able to interact with effectors, either individually or in a cooperative manner. The intrinsic GTPase activity of the  $\alpha$  subunit hydrolyzes the bound GTP to GDP. This returns the  $\alpha$  subunit to its inactive conformation and allows it to reassociate with the  $\beta$ - $\gamma$  complex, thus restoring the system to its resting state (Kaziro, supra). Some  $\alpha$  subunits show tissue-specific expression indicating a specialized signaling role (Dhanasekaran, supra).

The  $\alpha$ -s class of G-protein subunits is sensitive to ADP-ribosylation by pertussis toxin which uncouples the receptor:G-protein interaction. This uncoupling blocks signal transduction to receptors that decrease cAMP levels. cAMP levels regulate ion channels and activate phospholipases. The inhibitory  $\alpha$ -I class is also susceptible to modification by pertussis toxin, which prevents  $\alpha$ -I from lowering cAMP levels. Two novel classes of  $\alpha$  subunits refractory to pertussis toxin modification are  $\alpha$ -q, which activates phospholipase C, and  $\alpha$ -12, which has sequence homology with the Drosophila gene concertina and may contribute to the regulation of embryonic development (Simon, M.I. (1991) Science 252:802-808).

The mammalian G-protein  $\beta$  and  $\gamma$  subunits, each about 340 amino acids long, share more than 80% homology. The  $\beta$  subunit (also called  $\beta$ -transducin) contains seven repeating units, each about 43 amino acids long. This WD-repeat, or G-beta repeat motif, is found in a variety of proteins with regulatory function such as Sec13, a yeast WD repeat protein involved in vesicular traffic; coronin-2, a mammalian WD repeat protein involved in regulation of the actin cytoskeleton; and Bop1, a mammalian WD repeat protein involved in growth suppression (Garcia-Higuera, I. et al. (1998) J. Biol. Chem. 273:9041-9049; Okumura, M. et al. (1998) DNA Cell Biol. 17:779-787; Pestov, D.G. et al. (1998) Oncogene 17:3187-3197). The activity of the  $\beta$  and  $\gamma$  subunits may be regulated by other proteins such as calmodulin, phosducin, or the neural protein GAP 43 (Clapham, D.E. and E.J. Neer (1993) Nature 365:403-406). The  $\beta$  subunit sequences are highly conserved among species, suggesting that they perform a fundamentally important role in the organization and function of G-protein linked systems (Van der Voorn, L. and H.L. Ploegh (1992) FEBS Lett. 307:131-134).

Mutations and variant expression of  $\beta$ -transducin proteins are linked with various disorders. Mutations in LIS1, a subunit of the human platelet activating factor acetylhydrolase, cause Miller-Dieker lissencephaly. RACK1 binds activated protein kinase C, and RbAp48 binds retinoblastoma protein. CstF is required for polyadenylation of mammalian pre-mRNA in vitro and associates with subunits of cleavage-stimulating factor. Defects in the regulation of  $\beta$ -catenin contribute to the neoplastic transformation of human cells. The WD40 repeats of the human F-box protein  $\beta$ TrCP mediate binding to  $\beta$ -catenin, thus regulating the targeted degradation of  $\beta$ -catenin by ubiquitin ligase (Neer, E.J. et al. (1994) Nature 371:297-300; Hart, M. et al. (1999) Curr. Biol. 9:207-210).

The  $\gamma$  subunit sequences are more variable than those of the  $\beta$  subunits. They are often post-translationally modified by isoprenylation and carboxyl-methylation of a cysteine residue four amino

acids from the C-terminus. These modifications appear to be necessary for the interaction of the  $\beta$ - $\gamma$  dimer with the membrane and with other GTP-binding proteins. The  $\beta$ - $\gamma$  dimer has been shown to modulate the activity of adenylyl cyclase isoforms, phospholipase C, and some ion channels. It is involved in receptor phosphorylation via specific kinases and has been implicated in the p21ras-  
5 dependent activation of the MAP kinase cascade and the recognition of specific receptors by GTP-binding proteins (Clapham and Neer, supra).

G-proteins interact with a variety of effectors including adenylyl cyclase (Clapham and Neer, supra). The signaling pathway mediated by cAMP is mitogenic in hormone-dependent endocrine tissues such as adrenal cortex, thyroid, ovary, pituitary, and testes. Cancers in these tissues have been related  
10 to a mutationally activated form of a  $G\alpha_s$  known as the gsp (Gs protein) oncogene (Dhanasekaran, supra). Another effector is phosducin, a retinal phosphoprotein, which forms a specific complex with retinal G-protein  $\beta$  and  $\gamma$  subunits and modulates the ability of the  $\beta$ - $\gamma$  dimer to interact with retinal  $\alpha$  subunits (Clapham and Neer, supra). Additional G-protein effectors include RIN1 (Ras interaction/interference), which acts as an effector of H-Ras and interferes with the Ras signal  
15 transduction pathway; Rabin3, which associates with the Ras-like GTPase Rab3A; and Rhotekin, a protein that binds with, and inhibits, Rho GTPase activity (Han, L. and J. Colicelli (1995) Mol. Cell Biol. 15:1318-1323; Brondyk, W.H. et al. (1995) Mol. Cell Biol. 15:1137-1143; and Reid, T. et al. (1996) J. Biol. Chem. 27:13556-13560).

The low molecular weight GTP-binding proteins regulate cell growth, cell cycle control, protein  
20 secretion, and intracellular vesicle interaction. These GTP-binding proteins respond to extracellular signals from receptors and activating proteins by transducing mitogenic signals (Tavittian, A. (1995) C. R. Seances Soc. Biol. Fil. 189:7-12). Low molecular weight GTP-binding proteins consist of single polypeptides of 21-30kD which, like the  $\alpha$  subunit of heterotrimeric GTP-binding proteins, are able to bind to and hydrolyze GTP, thus cycling from an inactive to an active state. The intrinsic rate of GTP  
25 hydrolysis of these GTP-binding proteins is typically very slow, but it can be stimulated by several orders of magnitude by GTPase-activating proteins (GAPs), such as  $\beta$ 2-chimaerin (Geyer, M. and Wittinghofer, A. (1997) Curr. Opin. Struct. Biol. 7:786-792; Caloca, M. J. et al. (1997) J. Biol. Chem. 272:26488-26496).

Low molecular weight GTP-binding proteins play critical roles in cellular protein trafficking  
30 events, such as the translocation of proteins and soluble complexes from the cytosol to the membrane through an exchange of GDP for GTP (Ktistakis, N.T. (1998) BioEssays 20:495-504). In vesicle transport, the interaction between vesicle- and target- specific identifiers (v-SNAREs and tSNAREs) docks the vesicle to the acceptor membrane. The budding process is regulated by GTPases such as the closely related ADP ribosylation factors (ARFs) and SAR proteins, while GTPases such as Rab allow  
35 assembly of SNARE complexes and may play a role in removal of defective complexes (Rothman, J.E.

and F.T. Wieland (1996) Science 272:227-234). The rab proteins control the translocation of vesicles to and from membranes for protein localization, protein processing, and secretion. The rho GTP-binding proteins control signal transduction pathways that link growth factor receptors to actin polymerization which is necessary for normal cellular growth and division. The ran GTP-binding proteins are located in the nucleus of cells and have a key role in nuclear protein import, the control of DNA synthesis, and cell-cycle progression (Hall, A. (1990) Science 249:635-640; Scheffzek, K. et al. (1995) Nature 374:378-381).

The Ras proteins Ras1, Ras2 and G<sub>s</sub>α stimulate adenylyl cyclase (Kaziro, supra) which affects a broad array of cellular processes including determination of whether cells continue to grow or become terminally differentiated. Stimulation of cell surface receptors activates Ras which, in turn, activates cytoplasmic kinases. These kinases translocate to the nucleus and activate key transcription factors that control gene expression and protein synthesis (Barbacid, M. (1987) Annu. Rev. Biochem. 56:779-827; Treisman, R. (1994) Curr. Opin. Genet. Dev. 4:96-101). Mutant Ras-family proteins which bind but cannot hydrolyze GTP are permanently activated and are thus rendered oncogenic (Drivas, G.T. et al. (1990) Mol. Cell. Biol. 10:1793-1798).

Ras-like proteins have also been implicated in tumor suppression. For example, NOEY2, a novel gene encoding a Ras-like protein, is expressed in normal ovarian and breast epithelial cells. However, NOEY2 expression is reduced or abrogated in ovarian and breast carcinomas, suggesting a role for the NOEY2 gene product in tumor suppression (Yu, Y. et al. (1999) Proc. Natl. Acad. Sci. USA 96:214-219).

Irregularities in GTP-binding protein signaling cascades may result in abnormal activation of leukocytes and lymphocytes, leading to the tissue damage and destruction seen in many inflammatory and autoimmune diseases such as rheumatoid arthritis, biliary cirrhosis, hemolytic anemia, lupus erythematosus, and thyroiditis. Abnormal cell proliferation, including cyclic AMP-mediated stimulation of brain, thyroid, adrenal, and gonadal tissue proliferation is regulated by G proteins. Mutations in G<sub>s</sub>α subunits have been found in growth-hormone-secreting pituitary somatotroph tumors, hyperfunctioning thyroid adenomas, and ovarian and adrenal neoplasms (Meij, J.T.A. (1996) Mol. Cell. Biochem. 157:31-38; Aussel, supra).

The discovery of new GTP-binding associated proteins and the polynucleotides encoding them satisfies a need in the art by providing new compositions which are useful in the diagnosis, prevention, and treatment of immune system, reproductive, nervous system, and cell signaling disorders, and cell proliferative disorders including cancer.

#### SUMMARY OF THE INVENTION

The invention features purified polypeptides, GTP-binding associated proteins, referred to

collectively as "GBAP" and individually as "GBAP-1," "GBAP-2," "GBAP-3," "GBAP-4," "GBAP-5," "GBAP-6," "GBAP-7," "GBAP-8," "GBAP-9," "GBAP-10," "GBAP-11," "GBAP-12," "GBAP-13," "GBAP-14," "GBAP-15," "GBAP-16," "GBAP-17," "GBAP-18," "GBAP-19," "GBAP-20," "GBAP-21," "GBAP-22," "GBAP-23," "GBAP-24," "GBAP-25," "GBAP-26," "GBAP-27,"

5 "GBAP-28," "GBAP-29," "GBAP-30," "GBAP-31," "GBAP-32," "GBAP-33," "GBAP-34," "GBAP-35," "GBAP-36," "GBAP-37," "GBAP-38," "GBAP-39," "GBAP-40," "GBAP-41," "GBAP-42," "GBAP-43," "GBAP-44," "GBAP-45," "GBAP-46," "GBAP-47," "GBAP-48," "GBAP-49," "GBAP-50," "GBAP-51," "GBAP-52," "GBAP-53," "GBAP-54," "GBAP-55," "GBAP-56," "GBAP-57," "GBAP-58," "GBAP-59," "GBAP-60," "GBAP-61," "GBAP-62,"

10 "GBAP-63," "GBAP-64," "GBAP-65," and "GBAP-66." In one aspect, the invention provides an isolated polypeptide comprising an amino acid sequence selected from the group consisting of a) an amino acid sequence selected from the group consisting of SEQ ID NO:1-66, b) a naturally occurring amino acid sequence having at least 90% sequence identity to an amino acid sequence selected from the group consisting of SEQ ID NO:1-66, c) a biologically active fragment of an amino acid sequence

15 selected from the group consisting of SEQ ID NO:1-66, and d) an immunogenic fragment of an amino acid sequence selected from the group consisting of SEQ ID NO:1-66. In one alternative, the invention provides an isolated polypeptide comprising the amino acid sequence of SEQ ID NO:1-66.

The invention further provides an isolated polynucleotide encoding a polypeptide comprising an amino acid sequence selected from the group consisting of a) an amino acid sequence selected from the

20 group consisting of SEQ ID NO:1-66, b) a naturally occurring amino acid sequence having at least 90% sequence identity to an amino acid sequence selected from the group consisting of SEQ ID NO:1-66, c) a biologically active fragment of an amino acid sequence selected from the group consisting of SEQ ID NO:1-66, and d) an immunogenic fragment of an amino acid sequence selected from the group consisting of SEQ ID NO:1-66. In one alternative, the polynucleotide encodes a polypeptide selected

25 from the group consisting of SEQ ID NO:1-66. In another alternative, the polynucleotide is selected from the group consisting of SEQ ID NO:67-132.

Additionally, the invention provides a recombinant polynucleotide comprising a promoter sequence operably linked to a polynucleotide encoding a polypeptide comprising an amino acid sequence selected from the group consisting of a) an amino acid sequence selected from the group

30 consisting of SEQ ID NO:1-66, b) a naturally occurring amino acid sequence having at least 90% sequence identity to an amino acid sequence selected from the group consisting of SEQ ID NO:1-66, c) a biologically active fragment of an amino acid sequence selected from the group consisting of SEQ ID NO:1-66, and d) an immunogenic fragment of an amino acid sequence selected from the group consisting of SEQ ID NO:1-66. In one alternative, the invention provides a cell transformed with the

35 recombinant polynucleotide. In another alternative, the invention provides a transgenic organism

comprising the recombinant polynucleotide.

The invention also provides a method for producing a polypeptide comprising an amino acid sequence selected from the group consisting of a) an amino acid sequence selected from the group consisting of SEQ ID NO:1-66, b) a naturally occurring amino acid sequence having at least 90% sequence identity to an amino acid sequence selected from the group consisting of SEQ ID NO:1-66, c) a biologically active fragment of an amino acid sequence selected from the group consisting of SEQ ID NO:1-66, and d) an immunogenic fragment of an amino acid sequence selected from the group consisting of SEQ ID NO:1-66. The method comprises a) culturing a cell under conditions suitable for expression of the polypeptide, wherein said cell is transformed with a recombinant polynucleotide comprising a promoter sequence operably linked to a polynucleotide encoding the polypeptide, and b) recovering the polypeptide so expressed.

Additionally, the invention provides an isolated antibody which specifically binds to a polypeptide comprising an amino acid sequence selected from the group consisting of a) an amino acid sequence selected from the group consisting of SEQ ID NO:1-66, b) a naturally occurring amino acid sequence having at least 90% sequence identity to an amino acid sequence selected from the group consisting of SEQ ID NO:1-66, c) a biologically active fragment of an amino acid sequence selected from the group consisting of SEQ ID NO:1-66, and d) an immunogenic fragment of an amino acid sequence selected from the group consisting of SEQ ID NO:1-66.

The invention further provides an isolated polynucleotide comprising a polynucleotide sequence selected from the group consisting of a) a polynucleotide sequence selected from the group consisting of SEQ ID NO:67-132, b) a naturally occurring polynucleotide sequence having at least 70% sequence identity to a polynucleotide sequence selected from the group consisting of SEQ ID NO:67-132, c) a polynucleotide sequence complementary to a), d) a polynucleotide sequence complementary to b), and e) an RNA equivalent of a)-d). In one alternative, the polynucleotide comprises at least 60 contiguous nucleotides.

Additionally, the invention provides a method for detecting a target polynucleotide in a sample, said target polynucleotide having a sequence of a polynucleotide comprising a polynucleotide sequence selected from the group consisting of a) a polynucleotide sequence selected from the group consisting of SEQ ID NO:67-132, b) a naturally occurring polynucleotide sequence having at least 70% sequence identity to a polynucleotide sequence selected from the group consisting of SEQ ID NO:67-132, c) a polynucleotide sequence complementary to a), d) a polynucleotide sequence complementary to b), and e) an RNA equivalent of a)-d). The method comprises a) hybridizing the sample with a probe comprising at least 20 contiguous nucleotides comprising a sequence complementary to said target polynucleotide in the sample, and which probe specifically hybridizes to said target polynucleotide, under conditions whereby a hybridization complex is formed between said probe and said target polynucleotide or

fragments thereof, and b) detecting the presence or absence of said hybridization complex, and optionally, if present, the amount thereof. In one alternative, the probe comprises at least 60 contiguous nucleotides.

The invention further provides a method for detecting a target polynucleotide in a sample, said  
5 target polynucleotide having a sequence of a polynucleotide comprising a polynucleotide sequence selected from the group consisting of a) a polynucleotide sequence selected from the group consisting of SEQ ID NO:67-132, b) a naturally occurring polynucleotide sequence having at least 70% sequence identity to a polynucleotide sequence selected from the group consisting of SEQ ID NO:67-132, c) a polynucleotide sequence complementary to a), d) a polynucleotide sequence complementary to b), and e)  
10 an RNA equivalent of a)-d). The method comprises a) amplifying said target polynucleotide or fragment thereof using polymerase chain reaction amplification, and b) detecting the presence or absence of said amplified target polynucleotide or fragment thereof, and, optionally, if present, the amount thereof.

The invention further provides a composition comprising an effective amount of a polypeptide  
15 comprising an amino acid sequence selected from the group consisting of a) an amino acid sequence selected from the group consisting of SEQ ID NO:1-66, b) a naturally occurring amino acid sequence having at least 90% sequence identity to an amino acid sequence selected from the group consisting of SEQ ID NO:1-66, c) a biologically active fragment of an amino acid sequence selected from the group consisting of SEQ ID NO:1-66, and d) an immunogenic fragment of an amino acid sequence selected  
20 from the group consisting of SEQ ID NO:1-66, and a pharmaceutically acceptable excipient. In one embodiment, the composition comprises an amino acid sequence selected from the group consisting of SEQ ID NO:1-66. The invention additionally provides a method of treating a disease or condition associated with decreased expression of functional GBAP, comprising administering to a patient in need of such treatment the composition.

25 The invention also provides a method for screening a compound for effectiveness as an agonist of a polypeptide comprising an amino acid sequence selected from the group consisting of a) an amino acid sequence selected from the group consisting of SEQ ID NO:1-66, b) a naturally occurring amino acid sequence having at least 90% sequence identity to an amino acid sequence selected from the group consisting of SEQ ID NO:1-66, c) a biologically active fragment of an amino acid sequence  
30 selected from the group consisting of SEQ ID NO:1-66, and d) an immunogenic fragment of an amino acid sequence selected from the group consisting of SEQ ID NO:1-66. The method comprises a) exposing a sample comprising the polypeptide to a compound, and b) detecting agonist activity in the sample. In one alternative, the invention provides a composition comprising an agonist compound identified by the method and a pharmaceutically acceptable excipient. In another alternative, the  
35 invention provides a method of treating a disease or condition associated with decreased expression of

functional GBAP, comprising administering to a patient in need of such treatment the composition.

Additionally, the invention provides a method for screening a compound for effectiveness as an antagonist of a polypeptide comprising an amino acid sequence selected from the group consisting of a) an amino acid sequence selected from the group consisting of SEQ ID NO:1-66, b) a naturally occurring amino acid sequence having at least 90% sequence identity to an amino acid sequence selected from the group consisting of SEQ ID NO:1-66, c) a biologically active fragment of an amino acid sequence selected from the group consisting of SEQ ID NO:1-66, and d) an immunogenic fragment of an amino acid sequence selected from the group consisting of SEQ ID NO:1-66. The method comprises a) exposing a sample comprising the polypeptide to a compound, and b) detecting antagonist activity in the sample. In one alternative, the invention provides a composition comprising an antagonist compound identified by the method and a pharmaceutically acceptable excipient. In another alternative, the invention provides a method of treating a disease or condition associated with overexpression of functional GBAP, comprising administering to a patient in need of such treatment the composition.

The invention further provides a method of screening for a compound that specifically binds to a polypeptide comprising an amino acid sequence selected from the group consisting of a) an amino acid sequence selected from the group consisting of SEQ ID NO:1-66, b) a naturally occurring amino acid sequence having at least 90% sequence identity to an amino acid sequence selected from the group consisting of SEQ ID NO:1-66, c) a biologically active fragment of an amino acid sequence selected from the group consisting of SEQ ID NO:1-66, and d) an immunogenic fragment of an amino acid sequence selected from the group consisting of SEQ ID NO:1-66. The method comprises a) combining the polypeptide with at least one test compound under suitable conditions, and b) detecting binding of the polypeptide to the test compound, thereby identifying a compound that specifically binds to the polypeptide.

The invention further provides a method of screening for a compound that modulates the activity of a polypeptide comprising an amino acid sequence selected from the group consisting of a) an amino acid sequence selected from the group consisting of SEQ ID NO:1-66, b) a naturally occurring amino acid sequence having at least 90% sequence identity to an amino acid sequence selected from the group consisting of SEQ ID NO:1-66, c) a biologically active fragment of an amino acid sequence selected from the group consisting of SEQ ID NO:1-66, and d) an immunogenic fragment of an amino acid sequence selected from the group consisting of SEQ ID NO:1-66. The method comprises a) combining the polypeptide with at least one test compound under conditions permissive for the activity of the polypeptide, b) assessing the activity of the polypeptide in the presence of the test compound, and c) comparing the activity of the polypeptide in the presence of the test compound with the activity of the polypeptide in the absence of the test compound, wherein a

change in the activity of the polypeptide in the presence of the test compound is indicative of a compound that modulates the activity of the polypeptide.

The invention further provides a method for screening a compound for effectiveness in altering expression of a target polynucleotide, wherein said target polynucleotide comprises a sequence selected from the group consisting of SEQ ID NO:67-132, the method comprising a) exposing a sample comprising the target polynucleotide to a compound, and b) detecting altered expression of the target polynucleotide.

The invention further provides a method for assessing toxicity of a test compound, said method comprising a) treating a biological sample containing nucleic acids with the test compound; b) hybridizing the nucleic acids of the treated biological sample with a probe comprising at least 20 contiguous nucleotides of a polynucleotide comprising a polynucleotide sequence selected from the group consisting of i) a polynucleotide sequence selected from the group consisting of SEQ ID NO:67-132, ii) a naturally occurring polynucleotide sequence having at least 70% sequence identity to a polynucleotide sequence selected from the group consisting of SEQ ID NO:67-132, iii) a polynucleotide sequence complementary to i), iv) a polynucleotide sequence complementary to ii), and v) an RNA equivalent of i)-iv). Hybridization occurs under conditions whereby a specific hybridization complex is formed between said probe and a target polynucleotide in the biological sample, said target polynucleotide comprising a polynucleotide sequence selected from the group consisting of SEQ ID NO:67-132, ii) a naturally occurring polynucleotide sequence having at least 70% sequence identity to a polynucleotide sequence selected from the group consisting of SEQ ID NO:67-132, iii) a polynucleotide sequence complementary to i), iv) a polynucleotide sequence complementary to ii), and v) an RNA equivalent of i)-iv). Alternatively, the target polynucleotide comprises a fragment of the above polynucleotide sequence; c) quantifying the amount of hybridization complex; and d) comparing the amount of hybridization complex in the treated biological sample with the amount of hybridization complex in an untreated biological sample, wherein a difference in the amount of hybridization complex in the treated biological sample is indicative of toxicity of the test compound.

#### BRIEF DESCRIPTION OF THE TABLES

Table 1 shows polypeptide and nucleotide sequence identification numbers (SEQ ID NOs), clone identification numbers (clone IDs), cDNA libraries, and cDNA fragments used to assemble full-length sequences encoding GBAP.

Table 2 shows features of each polypeptide sequence, including potential motifs, homologous sequences, and methods, algorithms, and searchable databases used for analysis of GBAP.

Table 3 shows selected fragments of each nucleic acid sequence; the tissue-specific expression



patterns of each nucleic acid sequence as determined by northern analysis; diseases, disorders, or conditions associated with these tissues; and the vector into which each cDNA was cloned.

Table 4 describes the tissues used to construct the cDNA libraries from which cDNA clones encoding GBAP were isolated.

5 Table 5 shows the tools, programs, and algorithms used to analyze the polynucleotides and polypeptides of the invention, along with applicable descriptions, references, and threshold parameters.

## DESCRIPTION OF THE INVENTION

Before the present proteins, nucleotide sequences, and methods are described, it is understood  
10 that this invention is not limited to the particular machines, materials and methods described, as these may vary. It is also to be understood that the terminology used herein is for the purpose of describing particular embodiments only, and is not intended to limit the scope of the present invention which will be limited only by the appended claims.

It must be noted that as used herein and in the appended claims, the singular forms "a," "an,"  
15 and "the" include plural reference unless the context clearly dictates otherwise. Thus, for example, a reference to "a host cell" includes a plurality of such host cells, and a reference to "an antibody" is a reference to one or more antibodies and equivalents thereof known to those skilled in the art, and so forth.

Unless defined otherwise, all technical and scientific terms used herein have the same meanings  
20 as commonly understood by one of ordinary skill in the art to which this invention belongs. Although any machines, materials, and methods similar or equivalent to those described herein can be used to practice or test the present invention, the preferred machines, materials and methods are now described. All publications mentioned herein are cited for the purpose of describing and disclosing the cell lines, protocols, reagents and vectors which are reported in the publications and which might be used in  
25 connection with the invention. Nothing herein is to be construed as an admission that the invention is not entitled to antedate such disclosure by virtue of prior invention.

## DEFINITIONS

"GBAP" refers to the amino acid sequences of substantially purified GBAP obtained from any species, particularly a mammalian species, including bovine, ovine, porcine, murine, equine, and  
30 human, and from any source, whether natural, synthetic, semi-synthetic, or recombinant.

The term "agonist" refers to a molecule which intensifies or mimics the biological activity of GBAP. Agonists may include proteins, nucleic acids, carbohydrates, small molecules, or any other compound or composition which modulates the activity of GBAP either by directly interacting with GBAP or by acting on components of the biological pathway in which GBAP participates.

35 An "allelic variant" is an alternative form of the gene encoding GBAP. Allelic variants may

result from at least one mutation in the nucleic acid sequence and may result in altered mRNAs or in polypeptides whose structure or function may or may not be altered. A gene may have none, one, or many allelic variants of its naturally occurring form. Common mutational changes which give rise to allelic variants are generally ascribed to natural deletions, additions, or substitutions of nucleotides.

- 5 Each of these types of changes may occur alone, or in combination with the others, one or more times in a given sequence.

“Altered” nucleic acid sequences encoding GBAP include those sequences with deletions, insertions, or substitutions of different nucleotides, resulting in a polypeptide the same as GBAP or a polypeptide with at least one functional characteristic of GBAP. Included within this definition are

10 polymorphisms which may or may not be readily detectable using a particular oligonucleotide probe of the polynucleotide encoding GBAP, and improper or unexpected hybridization to allelic variants, with a locus other than the normal chromosomal locus for the polynucleotide sequence encoding GBAP. The encoded protein may also be “altered,” and may contain deletions, insertions, or substitutions of amino acid residues which produce a silent change and result in a functionally equivalent GBAP. Deliberate

15 amino acid substitutions may be made on the basis of similarity in polarity, charge, solubility, hydrophobicity, hydrophilicity, and/or the amphipathic nature of the residues, as long as the biological or immunological activity of GBAP is retained. For example, negatively charged amino acids may include aspartic acid and glutamic acid, and positively charged amino acids may include lysine and arginine. Amino acids with uncharged polar side chains having similar hydrophilicity values may

20 include: asparagine and glutamine; and serine and threonine. Amino acids with uncharged side chains having similar hydrophilicity values may include: leucine, isoleucine, and valine; glycine and alanine; and phenylalanine and tyrosine.

The terms “amino acid” and “amino acid sequence” refer to an oligopeptide, peptide, polypeptide, or protein sequence, or a fragment of any of these, and to naturally occurring or synthetic

25 molecules. Where “amino acid sequence” is recited to refer to a sequence of a naturally occurring protein molecule, “amino acid sequence” and like terms are not meant to limit the amino acid sequence to the complete native amino acid sequence associated with the recited protein molecule.

“Amplification” relates to the production of additional copies of a nucleic acid sequence.

Amplification is generally carried out using polymerase chain reaction (PCR) technologies well known

30 in the art.

The term “antagonist” refers to a molecule which inhibits or attenuates the biological activity of GBAP. Antagonists may include proteins such as antibodies, nucleic acids, carbohydrates, small molecules, or any other compound or composition which modulates the activity of GBAP either by directly interacting with GBAP or by acting on components of the biological pathway in which GBAP

35 participates.

The term "antibody" refers to intact immunoglobulin molecules as well as to fragments thereof, such as Fab, F(ab')<sub>2</sub>, and Fv fragments, which are capable of binding an epitopic determinant.

Antibodies that bind GBAP polypeptides can be prepared using intact polypeptides or using fragments containing small peptides of interest as the immunizing antigen. The polypeptide or oligopeptide used to immunize an animal (e.g., a mouse, a rat, or a rabbit) can be derived from the translation of RNA, or synthesized chemically, and can be conjugated to a carrier protein if desired. Commonly used carriers that are chemically coupled to peptides include bovine serum albumin, thyroglobulin, and keyhole limpet hemocyanin (KLH). The coupled peptide is then used to immunize the animal.

The term "antigenic determinant" refers to that region of a molecule (i.e., an epitope) that makes contact with a particular antibody. When a protein or a fragment of a protein is used to immunize a host animal, numerous regions of the protein may induce the production of antibodies which bind specifically to antigenic determinants (particular regions or three-dimensional structures on the protein). An antigenic determinant may compete with the intact antigen (i.e., the immunogen used to elicit the immune response) for binding to an antibody.

The term "antisense" refers to any composition capable of base-pairing with the "sense" (coding) strand of a specific nucleic acid sequence. Antisense compositions may include DNA; RNA; peptide nucleic acid (PNA); oligonucleotides having modified backbone linkages such as phosphorothioates, methylphosphonates, or benzylphosphonates; oligonucleotides having modified sugar groups such as 2'-methoxyethyl sugars or 2'-methoxyethoxy sugars; or oligonucleotides having modified bases such as 5-methyl cytosine, 2'-deoxyuracil, or 7-deaza-2'-deoxyguanosine. Antisense molecules may be produced by any method including chemical synthesis or transcription. Once introduced into a cell, the complementary antisense molecule base-pairs with a naturally occurring nucleic acid sequence produced by the cell to form duplexes which block either transcription or translation. The designation "negative" or "minus" can refer to the antisense strand, and the designation "positive" or "plus" can refer to the sense strand of a reference DNA molecule.

The term "biologically active" refers to a protein having structural, regulatory, or biochemical functions of a naturally occurring molecule. Likewise, "immunologically active" or "immunogenic" refers to the capability of the natural, recombinant, or synthetic GBAP, or of any oligopeptide thereof, to induce a specific immune response in appropriate animals or cells and to bind with specific antibodies.

"Complementary" describes the relationship between two single-stranded nucleic acid sequences that anneal by base-pairing. For example, 5'-AGT-3' pairs with its complement, 3'-TCA-5'.

A "composition comprising a given polynucleotide sequence" and a "composition comprising a given amino acid sequence" refer broadly to any composition containing the given polynucleotide or

amino acid sequence. The composition may comprise a dry formulation or an aqueous solution.

Compositions comprising polynucleotide sequences encoding GBAP or fragments of GBAP may be employed as hybridization probes. The probes may be stored in freeze-dried form and may be associated with a stabilizing agent such as a carbohydrate. In hybridizations, the probe may be

5 deployed in an aqueous solution containing salts (e.g., NaCl), detergents (e.g., sodium dodecyl sulfate; SDS), and other components (e.g., Denhardt's solution, dry milk, salmon sperm DNA, etc.).

"Consensus sequence" refers to a nucleic acid sequence which has been subjected to repeated DNA sequence analysis to resolve uncalled bases, extended using the XL-PCR kit (PE Biosystems, Foster City CA) in the 5' and/or the 3' direction, and resequenced, or which has been assembled from  
10 one or more overlapping cDNA, EST, or genomic DNA fragments using a computer program for fragment assembly, such as the GELVIEW fragment assembly system (GCG, Madison WI) or Phrap (University of Washington, Seattle WA). Some sequences have been both extended and assembled to produce the consensus sequence.

"Conservative amino acid substitutions" are those substitutions that are predicted to least  
15 interfere with the properties of the original protein, i.e., the structure and especially the function of the protein is conserved and not significantly changed by such substitutions. The table below shows amino acids which may be substituted for an original amino acid in a protein and which are regarded as conservative amino acid substitutions.

	Original Residue	Conservative Substitution
20	Ala	Gly, Ser
	Arg	His, Lys
	Asn	Asp, Gln, His
	Asp	Asn, Glu
	Cys	Ala, Ser
25	Gln	Asn, Glu, His
	Glu	Asp, Gln, His
	Gly	Ala
	His	Asn, Arg, Gln, Glu
	Ile	Leu, Val
30	Leu	Ile, Val
	Lys	Arg, Gln, Glu
	Met	Leu, Ile
	Phe	His, Met, Leu, Trp, Tyr
	Ser	Cys, Thr
35	Thr	Ser, Val
	Trp	Phe, Tyr
	Tyr	His, Phe, Trp
	Val	Ile, Leu, Thr

40 Conservative amino acid substitutions generally maintain (a) the structure of the polypeptide backbone in the area of the substitution, for example, as a beta sheet or alpha helical conformation, (b) the charge or hydrophobicity of the molecule at the site of the substitution, and/or (c) the bulk of the

side chain.

A "deletion" refers to a change in the amino acid or nucleotide sequence that results in the absence of one or more amino acid residues or nucleotides.

The term "derivative" refers to a chemically modified polynucleotide or polypeptide. Chemical  
5 modifications of a polynucleotide sequence can include, for example, replacement of hydrogen by an alkyl, acyl, hydroxyl, or amino group. A derivative polynucleotide encodes a polypeptide which retains at least one biological or immunological function of the natural molecule. A derivative polypeptide is one modified by glycosylation, pegylation, or any similar process that retains at least one biological or immunological function of the polypeptide from which it was derived.

10 A "detectable label" refers to a reporter molecule or enzyme that is capable of generating a measurable signal and is covalently or noncovalently joined to a polynucleotide or polypeptide.

A "fragment" is a unique portion of GBAP or the polynucleotide encoding GBAP which is identical in sequence to but shorter in length than the parent sequence. A fragment may comprise up to the entire length of the defined sequence, minus one nucleotide/amino acid residue. For example, a  
15 fragment may comprise from 5 to 1000 contiguous nucleotides or amino acid residues. A fragment used as a probe, primer, antigen, therapeutic molecule, or for other purposes, may be at least 5, 10, 15, 16, 20, 25, 30, 40, 50, 60, 75, 100, 150, 250 or at least 500 contiguous nucleotides or amino acid residues in length. Fragments may be preferentially selected from certain regions of a molecule. For example, a polypeptide fragment may comprise a certain length of contiguous amino acids selected  
20 from the first 250 or 500 amino acids (or first 25% or 50% of a polypeptide) as shown in a certain defined sequence. Clearly these lengths are exemplary, and any length that is supported by the specification, including the Sequence Listing, tables, and figures, may be encompassed by the present embodiments.

A fragment of SEQ ID NO:67-132 comprises a region of unique polynucleotide sequence that  
25 specifically identifies SEQ ID NO:67-132, for example, as distinct from any other sequence in the genome from which the fragment was obtained. A fragment of SEQ ID NO:67-132 is useful, for example, in hybridization and amplification technologies and in analogous methods that distinguish SEQ ID NO:67-132 from related polynucleotide sequences. The precise length of a fragment of SEQ ID NO:67-132 and the region of SEQ ID NO:67-132 to which the fragment corresponds are routinely  
30 determinable by one of ordinary skill in the art based on the intended purpose for the fragment.

A fragment of SEQ ID NO:1-66 is encoded by a fragment of SEQ ID NO:67-132. A fragment of SEQ ID NO:1-66 comprises a region of unique amino acid sequence that specifically identifies SEQ ID NO:1-66. For example, a fragment of SEQ ID NO:1-66 is useful as an immunogenic peptide for the development of antibodies that specifically recognize SEQ ID NO:1-66.  
35 The precise length of a fragment of SEQ ID NO:1-66 and the region of SEQ ID NO:1-66 to which the

fragment corresponds are routinely determinable by one of ordinary skill in the art based on the intended purpose for the fragment.

A "full-length" polynucleotide sequence is one containing at least a translation initiation codon (e.g., methionine) followed by an open reading frame and a translation termination codon. A "full-length" polynucleotide sequence encodes a "full-length" polypeptide sequence.

"Homology" refers to sequence similarity or, interchangeably, sequence identity, between two or more polynucleotide sequences or two or more polypeptide sequences.

The terms "percent identity" and "% identity," as applied to polynucleotide sequences, refer to the percentage of residue matches between at least two polynucleotide sequences aligned using a standardized algorithm. Such an algorithm may insert, in a standardized and reproducible way, gaps in the sequences being compared in order to optimize alignment between two sequences, and therefore achieve a more meaningful comparison of the two sequences.

Percent identity between polynucleotide sequences may be determined using the default parameters of the CLUSTAL V algorithm as incorporated into the MEGALIGN version 3.12e sequence alignment program. This program is part of the LASERGENE software package, a suite of molecular biological analysis programs (DNASTAR, Madison WI). CLUSTAL V is described in Higgins, D.G. and P.M. Sharp (1989) CABIOS 5:151-153 and in Higgins, D.G. et al. (1992) CABIOS 8:189-191. For pairwise alignments of polynucleotide sequences, the default parameters are set as follows: Ktuple=2, gap penalty=5, window=4, and "diagonals saved"=4. The "weighted" residue weight table is selected as the default. Percent identity is reported by CLUSTAL V as the "percent similarity" between aligned polynucleotide sequences.

Alternatively, a suite of commonly used and freely available sequence comparison algorithms is provided by the National Center for Biotechnology Information (NCBI) Basic Local Alignment Search Tool (BLAST) (Altschul, S.F. et al. (1990) J. Mol. Biol. 215:403-410), which is available from several sources, including the NCBI, Bethesda, MD, and on the Internet at <http://www.ncbi.nlm.nih.gov/BLAST/>. The BLAST software suite includes various sequence analysis programs including "blastn," that is used to align a known polynucleotide sequence with other polynucleotide sequences from a variety of databases. Also available is a tool called "BLAST 2 Sequences" that is used for direct pairwise comparison of two nucleotide sequences. "BLAST 2 Sequences" can be accessed and used interactively at <http://www.ncbi.nlm.nih.gov/gorf/bl2.html>. The "BLAST 2 Sequences" tool can be used for both blastn and blastp (discussed below). BLAST programs are commonly used with gap and other parameters set to default settings. For example, to compare two nucleotide sequences, one may use blastn with the "BLAST 2 Sequences" tool Version 2.0.12 (April-21-2000) set at default parameters. Such default parameters may be, for example:

*Matrix: BLOSUM62*

*Reward for match: 1*

*Penalty for mismatch: -2*

*Open Gap: 5 and Extension Gap: 2 penalties*

*Gap x drop-off: 50*

5 *Expect: 10*

*Word Size: 11*

*Filter: on*

Percent identity may be measured over the length of an entire defined sequence, for example, as defined by a particular SEQ ID number, or may be measured over a shorter length, for example, over  
10 the length of a fragment taken from a larger, defined sequence, for instance, a fragment of at least 20, at least 30, at least 40, at least 50, at least 70, at least 100, or at least 200 contiguous nucleotides. Such lengths are exemplary only, and it is understood that any fragment length supported by the sequences shown herein, in the tables, figures, or Sequence Listing, may be used to describe a length over which percentage identity may be measured.

15 Nucleic acid sequences that do not show a high degree of identity may nevertheless encode similar amino acid sequences due to the degeneracy of the genetic code. It is understood that changes in a nucleic acid sequence can be made using this degeneracy to produce multiple nucleic acid sequences that all encode substantially the same protein.

The phrases "percent identity" and "% identity," as applied to polypeptide sequences, refer to  
20 the percentage of residue matches between at least two polypeptide sequences aligned using a standardized algorithm. Methods of polypeptide sequence alignment are well-known. Some alignment methods take into account conservative amino acid substitutions. Such conservative substitutions, explained in more detail above, generally preserve the charge and hydrophobicity at the site of substitution, thus preserving the structure (and therefore function) of the polypeptide.

25 Percent identity between polypeptide sequences may be determined using the default parameters of the CLUSTAL V algorithm as incorporated into the MEGALIGN version 3.12e sequence alignment program (described and referenced above). For pairwise alignments of polypeptide sequences using CLUSTAL V, the default parameters are set as follows: Ktuple=1, gap penalty=3, window=5, and "diagonals saved"=5. The PAM250 matrix is selected as the default residue weight table. As with  
30 polynucleotide alignments, the percent identity is reported by CLUSTAL V as the "percent similarity" between aligned polypeptide sequence pairs.

Alternatively the NCBI BLAST software suite may be used. For example, for a pairwise comparison of two polypeptide sequences, one may use the "BLAST 2 Sequences" tool Version 2.0.12 (Apr-21-2000) with blastp set at default parameters. Such default parameters may be, for example:

35 *Matrix: BLOSUM62*

*Open Gap: 11 and Extension Gap: 1 penalties*

*Gap x drop-off: 50*

*Expect: 10*

*Word Size: 3*

5 *Filter: on*

Percent identity may be measured over the length of an entire defined polypeptide sequence, for example, as defined by a particular SEQ ID number, or may be measured over a shorter length, for example, over the length of a fragment taken from a larger, defined polypeptide sequence, for instance, a fragment of at least 15, at least 20, at least 30, at least 40, at least 50, at least 70 or at least 150  
10 contiguous residues. Such lengths are exemplary only, and it is understood that any fragment length supported by the sequences shown herein, in the tables, figures or Sequence Listing, may be used to describe a length over which percentage identity may be measured.

"Human artificial chromosomes" (HACs) are linear microchromosomes which may contain DNA sequences of about 6 kb to 10 Mb in size, and which contain all of the elements required for  
15 chromosome replication, segregation and maintenance.

The term "humanized antibody" refers to an antibody molecule in which the amino acid sequence in the non-antigen binding regions has been altered so that the antibody more closely resembles a human antibody, and still retains its original binding ability.

"Hybridization" refers to the process by which a polynucleotide strand anneals with a  
20 complementary strand through base pairing under defined hybridization conditions. Specific hybridization is an indication that two nucleic acid sequences share a high degree of complementarity. Specific hybridization complexes form under permissive annealing conditions and remain hybridized after the "washing" step(s). The washing step(s) is particularly important in determining the stringency of the hybridization process, with more stringent conditions allowing less non-specific binding, i.e.,  
25 binding between pairs of nucleic acid strands that are not perfectly matched. Permissive conditions for annealing of nucleic acid sequences are routinely determinable by one of ordinary skill in the art and may be consistent among hybridization experiments, whereas wash conditions may be varied among experiments to achieve the desired stringency, and therefore hybridization specificity. Permissive annealing conditions occur, for example, at 68°C in the presence of about 6 x SSC, about 1% (w/v)  
30 SDS, and about 100 µg/ml sheared, denatured salmon sperm DNA.

Generally, stringency of hybridization is expressed, in part, with reference to the temperature under which the wash step is carried out. Such wash temperatures are typically selected to be about 5°C to 20°C lower than the thermal melting point ( $T_m$ ) for the specific sequence at a defined ionic strength and pH. The  $T_m$  is the temperature (under defined ionic strength and pH) at which 50% of the  
35 target sequence hybridizes to a perfectly matched probe. An equation for calculating  $T_m$  and conditions



for nucleic acid hybridization are well known and can be found in Sambrook, J. et al., 1989, Molecular Cloning: A Laboratory Manual, 2<sup>nd</sup> ed., vol. 1-3, Cold Spring Harbor Press, Plainview NY; specifically see volume 2, chapter 9.

High stringency conditions for hybridization between polynucleotides of the present invention include wash conditions of 68°C in the presence of about 0.2 x SSC and about 0.1% SDS, for 1 hour. Alternatively, temperatures of about 65°C, 60°C, 55°C, or 42°C may be used. SSC concentration may be varied from about 0.1 to 2 x SSC, with SDS being present at about 0.1%. Typically, blocking reagents are used to block non-specific hybridization. Such blocking reagents include, for instance, sheared and denatured salmon sperm DNA at about 100-200 µg/ml. Organic solvent, such as formamide at a concentration of about 35-50% v/v, may also be used under particular circumstances, such as for RNA:DNA hybridizations. Useful variations on these wash conditions will be readily apparent to those of ordinary skill in the art. Hybridization, particularly under high stringency conditions, may be suggestive of evolutionary similarity between the nucleotides. Such similarity is strongly indicative of a similar role for the nucleotides and their encoded polypeptides.

The term "hybridization complex" refers to a complex formed between two nucleic acid sequences by virtue of the formation of hydrogen bonds between complementary bases. A hybridization complex may be formed in solution (e.g., C<sub>0</sub>t or R<sub>0</sub>t analysis) or formed between one nucleic acid sequence present in solution and another nucleic acid sequence immobilized on a solid support (e.g., paper, membranes, filters, chips, pins or glass slides, or any other appropriate substrate to which cells or their nucleic acids have been fixed).

The words "insertion" and "addition" refer to changes in an amino acid or nucleotide sequence resulting in the addition of one or more amino acid residues or nucleotides, respectively.

"Immune response" can refer to conditions associated with inflammation, trauma, immune disorders, or infectious or genetic disease, etc. These conditions can be characterized by expression of various factors, e.g., cytokines, chemokines, and other signaling molecules, which may affect cellular and systemic defense systems.

An "immunogenic fragment" is a polypeptide or oligopeptide fragment of GBAP which is capable of eliciting an immune response when introduced into a living organism, for example, a mammal. The term "immunogenic fragment" also includes any polypeptide or oligopeptide fragment of GBAP which is useful in any of the antibody production methods disclosed herein or known in the art.

The term "microarray" refers to an arrangement of a plurality of polynucleotides, polypeptides, or other chemical compounds on a substrate.

The terms "element" and "array element" refer to a polynucleotide, polypeptide, or other chemical compound having a unique and defined position on a microarray.

The term "modulate" refers to a change in the activity of GBAP. For example, modulation

may cause an increase or a decrease in protein activity, binding characteristics, or any other biological, functional, or immunological properties of GBAP.

The phrases "nucleic acid" and "nucleic acid sequence" refer to a nucleotide, oligonucleotide, polynucleotide, or any fragment thereof. These phrases also refer to DNA or RNA of genomic or synthetic origin which may be single-stranded or double-stranded and may represent the sense or the antisense strand, to peptide nucleic acid (PNA), or to any DNA-like or RNA-like material.

"Operably linked" refers to the situation in which a first nucleic acid sequence is placed in a functional relationship with a second nucleic acid sequence. For instance, a promoter is operably linked to a coding sequence if the promoter affects the transcription or expression of the coding sequence. Operably linked DNA sequences may be in close proximity or contiguous and, where necessary to join two protein coding regions, in the same reading frame.

"Peptide nucleic acid" (PNA) refers to an antisense molecule or anti-gene agent which comprises an oligonucleotide of at least about 5 nucleotides in length linked to a peptide backbone of amino acid residues ending in lysine. The terminal lysine confers solubility to the composition. PNAs preferentially bind complementary single stranded DNA or RNA and stop transcript elongation, and may be pegylated to extend their lifespan in the cell.

"Post-translational modification" of an GBAP may involve lipidation, glycosylation, phosphorylation, acetylation, racemization, proteolytic cleavage, and other modifications known in the art. These processes may occur synthetically or biochemically. Biochemical modifications will vary by cell type depending on the enzymatic milieu of GBAP.

"Probe" refers to nucleic acid sequences encoding GBAP, their complements, or fragments thereof, which are used to detect identical, allelic or related nucleic acid sequences. Probes are isolated oligonucleotides or polynucleotides attached to a detectable label or reporter molecule. Typical labels include radioactive isotopes, ligands, chemiluminescent agents, and enzymes. "Primers" are short nucleic acids, usually DNA oligonucleotides, which may be annealed to a target polynucleotide by complementary base-pairing. The primer may then be extended along the target DNA strand by a DNA polymerase enzyme. Primer pairs can be used for amplification (and identification) of a nucleic acid sequence, e.g., by the polymerase chain reaction (PCR).

Probes and primers as used in the present invention typically comprise at least 15 contiguous nucleotides of a known sequence. In order to enhance specificity, longer probes and primers may also be employed, such as probes and primers that comprise at least 20, 25, 30, 40, 50, 60, 70, 80, 90, 100, or at least 150 consecutive nucleotides of the disclosed nucleic acid sequences. Probes and primers may be considerably longer than these examples, and it is understood that any length supported by the specification, including the tables, figures, and Sequence Listing, may be used.

Methods for preparing and using probes and primers are described in the references, for

example Sambrook, J. et al., 1989, Molecular Cloning: A Laboratory Manual, 2<sup>nd</sup> ed., vol. 1-3, Cold Spring Harbor Press, Plainview NY; Ausubel, F.M. et al., 1987, Current Protocols in Molecular Biology, Greene Publ. Assoc. & Wiley-Intersciences, New York NY; Innis, M. et al., 1990, PCR Protocols, A Guide to Methods and Applications, Academic Press, San Diego CA. PCR primer pairs  
5 can be derived from a known sequence, for example, by using computer programs intended for that purpose such as Primer (Version 0.5, 1991, Whitehead Institute for Biomedical Research, Cambridge MA).

Oligonucleotides for use as primers are selected using software known in the art for such purpose. For example, OLIGO 4.06 software is useful for the selection of PCR primer pairs of up to  
10 100 nucleotides each, and for the analysis of oligonucleotides and larger polynucleotides of up to 5,000 nucleotides from an input polynucleotide sequence of up to 32 kilobases. Similar primer selection programs have incorporated additional features for expanded capabilities. For example, the PrimOU primer selection program (available to the public from the Genome Center at University of Texas South West Medical Center, Dallas TX) is capable of choosing specific primers from megabase sequences  
15 and is thus useful for designing primers on a genome-wide scope. The Primer3 primer selection program (available to the public from the Whitehead Institute/MIT Center for Genome Research, Cambridge MA) allows the user to input a "mispriming library," in which sequences to avoid as primer binding sites are user-specified. Primer3 is useful, in particular, for the selection of oligonucleotides for microarrays. (The source code for the latter two primer selection programs may also be obtained from  
20 their respective sources and modified to meet the user's specific needs.) The PrimeGen program (available to the public from the UK Human Genome Mapping Project Resource Centre, Cambridge UK) designs primers based on multiple sequence alignments, thereby allowing selection of primers that hybridize to either the most conserved or least conserved regions of aligned nucleic acid sequences. Hence, this program is useful for identification of both unique and conserved oligonucleotides and  
25 polynucleotide fragments. The oligonucleotides and polynucleotide fragments identified by any of the above selection methods are useful in hybridization technologies, for example, as PCR or sequencing primers, microarray elements, or specific probes to identify fully or partially complementary polynucleotides in a sample of nucleic acids. Methods of oligonucleotide selection are not limited to those described above.

30 A "recombinant nucleic acid" is a sequence that is not naturally occurring or has a sequence that is made by an artificial combination of two or more otherwise separated segments of sequence. This artificial combination is often accomplished by chemical synthesis or, more commonly, by the artificial manipulation of isolated segments of nucleic acids, e.g., by genetic engineering techniques such as those described in Sambrook, supra. The term recombinant includes nucleic acids that have  
35 been altered solely by addition, substitution, or deletion of a portion of the nucleic acid. Frequently, a

recombinant nucleic acid may include a nucleic acid sequence operably linked to a promoter sequence. Such a recombinant nucleic acid may be part of a vector that is used, for example, to transform a cell.

Alternatively, such recombinant nucleic acids may be part of a viral vector, e.g., based on a vaccinia virus, that could be used to vaccinate a mammal wherein the recombinant nucleic acid is  
5 expressed, inducing a protective immunological response in the mammal.

A "regulatory element" refers to a nucleic acid sequence usually derived from untranslated regions of a gene and includes enhancers, promoters, introns, and 5' and 3' untranslated regions (UTRs). Regulatory elements interact with host or viral proteins which control transcription, translation, or RNA stability.

10 "Reporter molecules" are chemical or biochemical moieties used for labeling a nucleic acid, amino acid, or antibody. Reporter molecules include radionuclides; enzymes; fluorescent, chemiluminescent, or chromogenic agents; substrates; cofactors; inhibitors; magnetic particles; and other moieties known in the art.

An "RNA equivalent," in reference to a DNA sequence, is composed of the same linear  
15 sequence of nucleotides as the reference DNA sequence with the exception that all occurrences of the nitrogenous base thymine are replaced with uracil, and the sugar backbone is composed of ribose instead of deoxyribose.

The term "sample" is used in its broadest sense. A sample suspected of containing nucleic acids encoding GBAP, or fragments thereof, or GBAP itself, may comprise a bodily fluid; an extract  
20 from a cell, chromosome, organelle, or membrane isolated from a cell; a cell; genomic DNA, RNA, or cDNA, in solution or bound to a substrate; a tissue; a tissue print; etc.

The terms "specific binding" and "specifically binding" refer to that interaction between a protein or peptide and an agonist, an antibody, an antagonist, a small molecule, or any natural or synthetic binding composition. The interaction is dependent upon the presence of a particular structure  
25 of the protein, e.g., the antigenic determinant or epitope, recognized by the binding molecule. For example, if an antibody is specific for epitope "A," the presence of a polypeptide comprising the epitope A, or the presence of free unlabeled A, in a reaction containing free labeled A and the antibody will reduce the amount of labeled A that binds to the antibody.

The term "substantially purified" refers to nucleic acid or amino acid sequences that are  
30 removed from their natural environment and are isolated or separated, and are at least 60% free, preferably at least 75% free, and most preferably at least 90% free from other components with which they are naturally associated.

A "substitution" refers to the replacement of one or more amino acid residues or nucleotides by different amino acid residues or nucleotides, respectively.

35 "Substrate" refers to any suitable rigid or semi-rigid support including membranes, filters,

chips, slides, wafers, fibers, magnetic or nonmagnetic beads, gels, tubing, plates, polymers, microparticles and capillaries. The substrate can have a variety of surface forms, such as wells, trenches, pins, channels and pores, to which polynucleotides or polypeptides are bound.

A "transcript image" refers to the collective pattern of gene expression by a particular cell type or tissue under given conditions at a given time.

"Transformation" describes a process by which exogenous DNA is introduced into a recipient cell. Transformation may occur under natural or artificial conditions according to various methods well known in the art, and may rely on any known method for the insertion of foreign nucleic acid sequences into a prokaryotic or eukaryotic host cell. The method for transformation is selected based on the type of host cell being transformed and may include, but is not limited to, bacteriophage or viral infection, electroporation, heat shock, lipofection, and particle bombardment. The term "transformed" cells includes stably transformed cells in which the inserted DNA is capable of replication either as an autonomously replicating plasmid or as part of the host chromosome, as well as transiently transformed cells which express the inserted DNA or RNA for limited periods of time.

A "transgenic organism," as used herein, is any organism, including but not limited to animals and plants, in which one or more of the cells of the organism contains heterologous nucleic acid introduced by way of human intervention, such as by transgenic techniques well known in the art. The nucleic acid is introduced into the cell, directly or indirectly by introduction into a precursor of the cell, by way of deliberate genetic manipulation, such as by microinjection or by infection with a recombinant virus. The term genetic manipulation does not include classical cross-breeding, or in vitro fertilization, but rather is directed to the introduction of a recombinant DNA molecule. The transgenic organisms contemplated in accordance with the present invention include bacteria, cyanobacteria, fungi, plants, and animals. The isolated DNA of the present invention can be introduced into the host by methods known in the art, for example infection, transfection, transformation or transconjugation. Techniques for transferring the DNA of the present invention into such organisms are widely known and provided in references such as Sambrook et al. (1989), supra.

A "variant" of a particular nucleic acid sequence is defined as a nucleic acid sequence having at least 40% sequence identity to the particular nucleic acid sequence over a certain length of one of the nucleic acid sequences using blastn with the "BLAST 2 Sequences" tool Version 2.0.9 (May-07-1999) set at default parameters. Such a pair of nucleic acids may show, for example, at least 50%, at least 60%, at least 70%, at least 80%, at least 85%, at least 90%, at least 95% or at least 98% or greater sequence identity over a certain defined length. A variant may be described as, for example, an "allelic" (as defined above), "splice," "species," or "polymorphic" variant. A splice variant may have significant identity to a reference molecule, but will generally have a greater or lesser number of polynucleotides

due to alternative splicing of exons during mRNA processing. The corresponding polypeptide may possess additional functional domains or lack domains that are present in the reference molecule. Species variants are polynucleotide sequences that vary from one species to another. The resulting polypeptides generally will have significant amino acid identity relative to each other. A polymorphic variant is a variation in the polynucleotide sequence of a particular gene between individuals of a given species. Polymorphic variants also may encompass "single nucleotide polymorphisms" (SNPs) in which the polynucleotide sequence varies by one nucleotide base. The presence of SNPs may be indicative of, for example, a certain population, a disease state, or a propensity for a disease state.

A "variant" of a particular polypeptide sequence is defined as a polypeptide sequence having at least 40% sequence identity to the particular polypeptide sequence over a certain length of one of the polypeptide sequences using blastp with the "BLAST 2 Sequences" tool Version 2.0.9 (May-07-1999) set at default parameters. Such a pair of polypeptides may show, for example, at least 50%, at least 60%, at least 70%, at least 80%, at least 90%, at least 95%, or at least 98% or greater sequence identity over a certain defined length of one of the polypeptides.

## 15 THE INVENTION

The invention is based on the discovery of new human GTP-binding associated proteins (GBAP), the polynucleotides encoding GBAP, and the use of these compositions for the diagnosis, treatment, or prevention of immune system, reproductive, nervous system, and cell signaling disorders, and cell proliferative disorders including cancer.

20 Table 1 lists the Incyte clones used to assemble full length nucleotide sequences encoding GBAP. Columns 1 and 2 show the sequence identification numbers (SEQ ID NOs) of the polypeptide and nucleotide sequences, respectively. Column 3 shows the clone IDs of the Incyte clones in which nucleic acids encoding each GBAP were identified, and column 4 shows the cDNA libraries from which these clones were isolated. Column 5 shows Incyte clones and their corresponding cDNA libraries. Clones for which cDNA libraries are not indicated were derived from pooled cDNA libraries. In some cases, GenBank sequence identifiers are also shown in column 5. The Incyte clones and GenBank cDNA sequences, where indicated, in column 5 were used to assemble the consensus nucleotide sequence of each GBAP and are useful as fragments in hybridization technologies.

The columns of Table 2 show various properties of each of the polypeptides of the invention: column 1 references the SEQ ID NO; column 2 shows the number of amino acid residues in each polypeptide; column 3 shows potential phosphorylation sites; column 4 shows potential glycosylation sites; column 5 shows the amino acid residues comprising signature sequences and motifs; column 6 shows homologous sequences as identified by BLAST analysis; and column 7 shows analytical methods and in some cases, searchable databases to which the analytical methods were applied. The methods of column 7 were used to characterize each polypeptide through sequence homology and protein motifs.

The columns of Table 3 show the tissue-specificity and diseases, disorders, or conditions associated with nucleotide sequences encoding GBAP. The first column of Table 3 lists the nucleotide SEQ ID NOs. Column 2 lists fragments of the nucleotide sequences of column 1. These fragments are useful, for example, in hybridization or amplification technologies to identify SEQ ID NO:67-132 and to distinguish between SEQ ID NO:67-132 and related polynucleotide sequences. The polypeptides encoded by these fragments are useful, for example, as immunogenic peptides. Column 3 lists tissue categories which express GBAP as a fraction of total tissues expressing GBAP. Column 4 lists diseases, disorders, or conditions associated with those tissues expressing GBAP as a fraction of total tissues expressing GBAP. Column 5 lists the vectors used to subclone each cDNA library. Of particular note is the expression of SEQ ID NO:84 in lung tissues, and the tissue-specific expression of SEQ ID NO:132. Over 90% of tissues expressing SEQ ID NO:132 are derived from the nervous system, particularly the brain.

The columns of Table 4 show descriptions of the tissues used to construct the cDNA libraries from which cDNA clones encoding GBAP were isolated. Column 1 references the nucleotide SEQ ID NOs, column 2 shows the cDNA libraries from which these clones were isolated, and column 3 shows the tissue origins and other descriptive information relevant to the cDNA libraries in column 2.

SEQ ID NO:70 maps to chromosome 7 within the interval from 111.6 to 123.4 centiMorgans. This interval contains a gene that is down regulated in adenoma. SEQ ID NO:74 maps to chromosome 11 within the interval from 104.8 to 123.5 centiMorgans. This interval contains a gene associated with the cerebellar degenerative disorder, ataxia telangiectasia. SEQ ID NO:75 maps to chromosome 17 within the interval from 62.9 to 65.0 centiMorgans. SEQ ID NO:77 maps to chromosome 3 within the interval from 12.9 to 16.5 centiMorgans. SEQ ID NO:80 maps to chromosome 9 within the interval from 42.0 to 57.3 centiMorgans. SEQ ID NO:86 maps to chromosome 1 within the interval from 159.6 to 164.1 centiMorgans. SEQ ID NO:87 maps to chromosome 11 within the interval from 147.2 to 151.6. SEQ ID NO:90 maps to chromosome 1 within the interval from 219.2 to 223.0 centiMorgans. This interval contains a gene encoding a RAB interacting protein. SEQ ID NO:92 and SEQ ID NO:106 both map to chromosome 1 within the interval from 48.8 to 81.6 centiMorgans. This interval also contains genes associated with familial hypercholesterolemia, glucose transport defect, infantile hypophosphatasia, infantile neuronal ceroid lipofuscinosis, Kostmann disease, multiple epiphyseal dysplasia, porphyria cutanea tarda, and T-cell acute lymphocytic leukemia 1. SEQ ID NO:93 maps to chromosome 12 within the interval from 76.5 to 87.6 centiMorgans. This interval also contains genes associated with mucopolysaccharidosis type IIID, pseudovitamin D deficiency rickets, and renal amyloidosis. SEQ ID NO:94 and SEQ ID NO:109 both map to chromosome 1 within the interval from 143.1 to 146.6 centiMorgans, to chromosome 14 within the interval from 46.8 to 50.9 centiMorgans, to chromosome 16 within the interval from 88.1 to 90.2 centiMorgans, and to chromosome 19 within the

interval from 58.7 to 97.5 centiMorgans. The interval on chromosome 14 from 46.8 to 50.9 centiMorgans also contains a gene associated with dopa-responsive dystonia. The interval on chromosome 19 from 58.7 to 97.5 centiMorgans also contains genes associated with colorectal cancer, DNA ligase I deficiency, glutaricaciduria IIB, myotonic dystrophy, renal amyloidosis, T-cell acute lymphoblastic leukemia, and xeroderma pigmentosum D. SEQ ID NO:97 maps to chromosome 2 within the interval from 236.2 to 269.5 centiMorgans. This interval also contains genes associated with Crigler-Najjar syndrome, familial hypercholesterolemia, Oguchi disease, and primary hyperoxaluria. SEQ ID NO:101 maps to chromosome 2 within the interval from 225.6 to 233.1 centiMorgans, to chromosome 6 within the interval from 132.7 to 144.4 centiMorgans, and to chromosome 11 within the interval from 117.9 to 120.8 centiMorgans. The interval on chromosome 2 from 225.6 to 233.1 centiMorgans also contains a gene associated with Waardenburg syndrome 1. The interval on chromosome 6 from 132.7 to 144.4 centiMorgans also contains genes associated with familial disseminated atypical mycobacterial infection and rhizomelic chondrodysplasia punctata. The interval on chromosome 11 from 117.9 to 120.8 centiMorgans also contains a gene associated with acute intermittent porphyria. SEQ ID NO:111 maps to chromosome 19 within the interval from 35.5 to 49.4 centiMorgans, to chromosome 1 within the interval from the p-terminus to 16.4 centiMorgans, and to chromosome 11 within the interval from 147.2 centiMorgans to the q-terminus. SEQ ID NO:112 maps to chromosome 19 within the interval from 41.7 to 49.4 centiMorgans. SEQ ID NO:113 maps to chromosome 9 within the interval from 136.2 to 163.0 centiMorgans. SEQ ID NO:115 maps to chromosome 14 within the interval from 95.5 to 103.7 centiMorgans and to the X chromosome (23) within the interval from the p-terminus to 55.5 centiMorgans. SEQ ID NO:117 maps to chromosome 13 at 46.9 centiMorgans. SEQ ID NO:118 maps to chromosome 1 within the interval from 16.4 to 22.9 centiMorgans. SEQ ID NO:121 maps to chromosome 12 within the interval from 116.6 to 118.9 centiMorgans. SEQ ID NO:128 maps to chromosome 1 within the interval from the p-terminus to 16.4 centiMorgans.

The invention also encompasses GBAP variants. A preferred GBAP variant is one which has at least about 80%, or alternatively at least about 90%, or even at least about 95% amino acid sequence identity to the GBAP amino acid sequence, and which contains at least one functional or structural characteristic of GBAP.

The invention also encompasses polynucleotides which encode GBAP. In a particular embodiment, the invention encompasses a polynucleotide sequence comprising a sequence selected from the group consisting of SEQ ID NO:67-132, which encodes GBAP. The polynucleotide sequences of SEQ ID NO:67-132, as presented in the Sequence Listing, embrace the equivalent RNA sequences, wherein occurrences of the nitrogenous base thymine are replaced with uracil, and the sugar backbone is composed of ribose instead of deoxyribose.



The invention also encompasses a variant of a polynucleotide sequence encoding GBAP. In particular, such a variant polynucleotide sequence will have at least about 70%, or alternatively at least about 85%, or even at least about 95% polynucleotide sequence identity to the polynucleotide sequence encoding GBAP. A particular aspect of the invention encompasses a variant of a polynucleotide  
5 sequence comprising a sequence selected from the group consisting of SEQ ID NO:67-132 which has at least about 70%, or alternatively at least about 85%, or even at least about 95% polynucleotide sequence identity to a nucleic acid sequence selected from the group consisting of SEQ ID NO:67-132. Any one of the polynucleotide variants described above can encode an amino acid sequence which contains at least one functional or structural characteristic of GBAP.

10 It will be appreciated by those skilled in the art that as a result of the degeneracy of the genetic code, a multitude of polynucleotide sequences encoding GBAP, some bearing minimal similarity to the polynucleotide sequences of any known and naturally occurring gene, may be produced. Thus, the invention contemplates each and every possible variation of polynucleotide sequence that could be made by selecting combinations based on possible codon choices. These combinations are made in  
15 accordance with the standard triplet genetic code as applied to the polynucleotide sequence of naturally occurring GBAP, and all such variations are to be considered as being specifically disclosed.

Although nucleotide sequences which encode GBAP and its variants are generally capable of hybridizing to the nucleotide sequence of the naturally occurring GBAP under appropriately selected conditions of stringency, it may be advantageous to produce nucleotide sequences encoding GBAP or its  
20 derivatives possessing a substantially different codon usage, e.g., inclusion of non-naturally occurring codons. Codons may be selected to increase the rate at which expression of the peptide occurs in a particular prokaryotic or eukaryotic host in accordance with the frequency with which particular codons are utilized by the host. Other reasons for substantially altering the nucleotide sequence encoding GBAP and its derivatives without altering the encoded amino acid sequences include the production of  
25 RNA transcripts having more desirable properties, such as a greater half-life, than transcripts produced from the naturally occurring sequence.

The invention also encompasses production of DNA sequences which encode GBAP and GBAP derivatives, or fragments thereof, entirely by synthetic chemistry. After production, the synthetic sequence may be inserted into any of the many available expression vectors and cell systems  
30 using reagents well known in the art. Moreover, synthetic chemistry may be used to introduce mutations into a sequence encoding GBAP or any fragment thereof.

Also encompassed by the invention are polynucleotide sequences that are capable of hybridizing to the claimed polynucleotide sequences, and, in particular, to those shown in SEQ ID NO:67-132 and fragments thereof under various conditions of stringency. (See, e.g., Wahl, G.M. and  
35 S.L. Berger (1987) *Methods Enzymol.* 152:399-407; Kimmel, A.R. (1987) *Methods Enzymol.*

152:507-511.) Hybridization conditions, including annealing and wash conditions, are described in "Definitions."

Methods for DNA sequencing are well known in the art and may be used to practice any of the embodiments of the invention. The methods may employ such enzymes as the Klenow fragment of DNA polymerase I, SEQUENASE (US Biochemical, Cleveland OH), Taq polymerase (PE Biosystems, Foster City CA), thermostable T7 polymerase (Amersham Pharmacia Biotech, Piscataway NJ), or combinations of polymerases and proofreading exonucleases such as those found in the ELONGASE amplification system (Life Technologies, Gaithersburg MD). Preferably, sequence preparation is automated with machines such as the MICROLAB 2200 liquid transfer system (Hamilton, Reno NV), PTC200 thermal cycler (MJ Research, Watertown MA) and ABI CATALYST 800 thermal cycler (PE Biosystems). Sequencing is then carried out using either the ABI 373 or 377 DNA sequencing system (PE Biosystems), the MEGABACE 1000 DNA sequencing system (Molecular Dynamics, Sunnyvale CA), or other systems known in the art. The resulting sequences are analyzed using a variety of algorithms which are well known in the art. (See, e.g., Ausubel, F.M. (1997) Short Protocols in Molecular Biology, John Wiley & Sons, New York NY, unit 7.7; Meyers, R.A. (1995) Molecular Biology and Biotechnology, Wiley VCH, New York NY, pp. 856-853.)

The nucleic acid sequences encoding GBAP may be extended utilizing a partial nucleotide sequence and employing various PCR-based methods known in the art to detect upstream sequences, such as promoters and regulatory elements. For example, one method which may be employed, restriction-site PCR, uses universal and nested primers to amplify unknown sequence from genomic DNA within a cloning vector. (See, e.g., Sarkar, G. (1993) PCR Methods Applic. 2:318-322.) Another method, inverse PCR, uses primers that extend in divergent directions to amplify unknown sequence from a circularized template. The template is derived from restriction fragments comprising a known genomic locus and surrounding sequences. (See, e.g., Triglia, T. et al. (1988) Nucleic Acids Res. 16:8186.) A third method, capture PCR, involves PCR amplification of DNA fragments adjacent to known sequences in human and yeast artificial chromosome DNA. (See, e.g., Lagerstrom, M. et al. (1991) PCR Methods Applic. 1:111-119.) In this method, multiple restriction enzyme digestions and ligations may be used to insert an engineered double-stranded sequence into a region of unknown sequence before performing PCR. Other methods which may be used to retrieve unknown sequences are known in the art. (See, e.g., Parker, J.D. et al. (1991) Nucleic Acids Res. 19:3055-3060.) Additionally, one may use PCR, nested primers, and PROMOTERFINDER libraries (Clontech, Palo Alto CA) to walk genomic DNA. This procedure avoids the need to screen libraries and is useful in finding intron/exon junctions. For all PCR-based methods, primers may be designed using commercially available software, such as OLIGO 4.06 Primer Analysis software (National Biosciences, Plymouth MN) or another appropriate program, to be about 22 to 30 nucleotides in length, to have a

GC content of about 50% or more, and to anneal to the template at temperatures of about 68°C to 72°C.

When screening for full-length cDNAs, it is preferable to use libraries that have been size-selected to include larger cDNAs. In addition, random-primed libraries, which often include sequences containing the 5' regions of genes, are preferable for situations in which an oligo d(T) library does not yield a full-length cDNA. Genomic libraries may be useful for extension of sequence into 5' non-transcribed regulatory regions.

Capillary electrophoresis systems which are commercially available may be used to analyze the size or confirm the nucleotide sequence of sequencing or PCR products. In particular, capillary sequencing may employ flowable polymers for electrophoretic separation, four different nucleotide-specific, laser-stimulated fluorescent dyes, and a charge coupled device camera for detection of the emitted wavelengths. Output/light intensity may be converted to electrical signal using appropriate software (e.g., GENOTYPER and SEQUENCE NAVIGATOR, PE Biosystems), and the entire process from loading of samples to computer analysis and electronic data display may be computer controlled. Capillary electrophoresis is especially preferable for sequencing small DNA fragments which may be present in limited amounts in a particular sample.

In another embodiment of the invention, polynucleotide sequences or fragments thereof which encode GBAP may be cloned in recombinant DNA molecules that direct expression of GBAP, or fragments or functional equivalents thereof, in appropriate host cells. Due to the inherent degeneracy of the genetic code, other DNA sequences which encode substantially the same or a functionally equivalent amino acid sequence may be produced and used to express GBAP.

The nucleotide sequences of the present invention can be engineered using methods generally known in the art in order to alter GBAP-encoding sequences for a variety of purposes including, but not limited to, modification of the cloning, processing, and/or expression of the gene product. DNA shuffling by random fragmentation and PCR reassembly of gene fragments and synthetic oligonucleotides may be used to engineer the nucleotide sequences. For example, oligonucleotide-mediated site-directed mutagenesis may be used to introduce mutations that create new restriction sites, alter glycosylation patterns, change codon preference, produce splice variants, and so forth.

The nucleotides of the present invention may be subjected to DNA shuffling techniques such as MOLECULARBREEDING (Maxygen Inc., Santa Clara CA; described in U.S. Patent Number 5,837,458; Chang, C.-C. et al. (1999) Nat. Biotechnol. 17:793-797; Christians, F.C. et al. (1999) Nat. Biotechnol. 17:259-264; and Cramer, A. et al. (1996) Nat. Biotechnol. 14:315-319) to alter or improve the biological properties of GBAP, such as its biological or enzymatic activity or its ability to bind to other molecules or compounds. DNA shuffling is a process by which a library of gene variants is produced using PCR-mediated recombination of gene fragments. The library is then

subjected to selection or screening procedures that identify those gene variants with the desired properties. These preferred variants may then be pooled and further subjected to recursive rounds of DNA shuffling and selection/screening. Thus, genetic diversity is created through "artificial" breeding and rapid molecular evolution. For example, fragments of a single gene containing random point mutations may be recombined, screened, and then reshuffled until the desired properties are optimized. Alternatively, fragments of a given gene may be recombined with fragments of homologous genes in the same gene family, either from the same or different species, thereby maximizing the genetic diversity of multiple naturally occurring genes in a directed and controllable manner.

10 In another embodiment, sequences encoding GBAP may be synthesized, in whole or in part, using chemical methods well known in the art. (See, e.g., Caruthers, M.H. et al. (1980) *Nucleic Acids Symp. Ser. 7*:215-223; and Horn, T. et al. (1980) *Nucleic Acids Symp. Ser. 7*:225-232.) Alternatively, GBAP itself or a fragment thereof may be synthesized using chemical methods. For example, peptide synthesis can be performed using various solution-phase or solid-phase techniques. (See, e.g., Creighton, T. (1984) Proteins, Structures and Molecular Properties, WH Freeman, New York NY, pp. 15 55-60; and Roberge, J.Y. et al. (1995) *Science* 269:202-204.) Automated synthesis may be achieved using the ABI 431A peptide synthesizer (PE Biosystems). Additionally, the amino acid sequence of GBAP, or any part thereof, may be altered during direct synthesis and/or combined with sequences from other proteins, or any part thereof, to produce a variant polypeptide or a polypeptide having a sequence of a naturally occurring polypeptide.

The peptide may be substantially purified by preparative high performance liquid chromatography. (See, e.g., Chiez, R.M. and F.Z. Regnier (1990) *Methods Enzymol.* 182:392-421.) The composition of the synthetic peptides may be confirmed by amino acid analysis or by sequencing. (See, e.g., Creighton, supra, pp. 28-53.)

25 In order to express a biologically active GBAP, the nucleotide sequences encoding GBAP or derivatives thereof may be inserted into an appropriate expression vector, i.e., a vector which contains the necessary elements for transcriptional and translational control of the inserted coding sequence in a suitable host. These elements include regulatory sequences, such as enhancers, constitutive and inducible promoters, and 5' and 3' untranslated regions in the vector and in polynucleotide sequences encoding GBAP. Such elements may vary in their strength and specificity. Specific initiation signals may also be used to achieve more efficient translation of sequences encoding GBAP. Such signals include the ATG initiation codon and adjacent sequences, e.g. the Kozak sequence. In cases where sequences encoding GBAP and its initiation codon and upstream regulatory sequences are inserted into the appropriate expression vector, no additional transcriptional or translational control signals may be 35 needed. However, in cases where only coding sequence, or a fragment thereof, is inserted, exogenous

translational control signals including an in-frame ATG initiation codon should be provided by the vector. Exogenous translational elements and initiation codons may be of various origins, both natural and synthetic. The efficiency of expression may be enhanced by the inclusion of enhancers appropriate for the particular host cell system used. (See, e.g., Scharf, D. et al. (1994) *Results Probl. Cell Differ.*

5 20:125-162.)

Methods which are well known to those skilled in the art may be used to construct expression vectors containing sequences encoding GBAP and appropriate transcriptional and translational control elements. These methods include in vitro recombinant DNA techniques, synthetic techniques, and in vivo genetic recombination. (See, e.g., Sambrook, J. et al. (1989) Molecular Cloning, A Laboratory  
10 Manual, Cold Spring Harbor Press, Plainview NY, ch. 4, 8, and 16-17; Ausubel, F.M. et al. (1995) Current Protocols in Molecular Biology, John Wiley & Sons, New York NY, ch. 9, 13, and 16.)

A variety of expression vector/host systems may be utilized to contain and express sequences encoding GBAP. These include, but are not limited to, microorganisms such as bacteria transformed with recombinant bacteriophage, plasmid, or cosmid DNA expression vectors; yeast transformed with  
15 yeast expression vectors; insect cell systems infected with viral expression vectors (e.g., baculovirus); plant cell systems transformed with viral expression vectors (e.g., cauliflower mosaic virus, CaMV, or tobacco mosaic virus, TMV) or with bacterial expression vectors (e.g., Ti or pBR322 plasmids); or animal cell systems. (See, e.g., Sambrook, supra; Ausubel, supra; Van Heeke, G. and S.M. Schuster (1989) *J. Biol. Chem.* 264:5503-5509; Bitter, G.A. et al. (1987) *Methods Enzymol.* 153:516-544;  
20 Scorer, C.A. et al. (1994) *Bio/Technology* 12:181-184; Engelhard, E.K. et al. (1994) *Proc. Natl. Acad. Sci. USA* 91:3224-3227; Sandig, V. et al. (1996) *Hum. Gene Ther.* 7:1937-1945; Takamatsu, N. (1987) *EMBO J.* 6:307-311; Coruzzi, G. et al. (1984) *EMBO J.* 3:1671-1680; Broglie, R. et al. (1984) *Science* 224:838-843; Winter, J. et al. (1991) *Results Probl. Cell Differ.* 17:85-105; The McGraw Hill Yearbook of Science and Technology (1992) McGraw Hill, New York NY, pp.  
25 191-196; Logan, J. and T. Shenk (1984) *Proc. Natl. Acad. Sci. USA* 81:3655-3659; and Harrington, J.J. et al. (1997) *Nat. Genet.* 15:345-355.) Expression vectors derived from retroviruses, adenoviruses, or herpes or vaccinia viruses, or from various bacterial plasmids; may be used for delivery of nucleotide sequences to the targeted organ, tissue, or cell population. (See, e.g., Di Nicola, M. et al. (1998) *Cancer Gen. Ther.* 5(6):350-356; Yu, M. et al., (1993) *Proc. Natl. Acad. Sci.*  
30 *USA* 90(13):6340-6344; Buller, R.M. et al. (1985) *Nature* 317(6040):813-815; McGregor, D.P. et al. (1994) *Mol. Immunol.* 31(3):219-226; and Verma, I.M. and N. Somia (1997) *Nature* 389:239-242.) The invention is not limited by the host cell employed.

In bacterial systems, a number of cloning and expression vectors may be selected depending upon the use intended for polynucleotide sequences encoding GBAP. For example, routine cloning,  
35 subcloning, and propagation of polynucleotide sequences encoding GBAP can be achieved using a

multifunctional E. coli vector such as PBLUESCRIPT (Stratagene, La Jolla CA) or PSPORT1 plasmid (Life Technologies). Ligation of sequences encoding GBAP into the vector's multiple cloning site disrupts the *lacZ* gene, allowing a colorimetric screening procedure for identification of transformed bacteria containing recombinant molecules. In addition, these vectors may be useful for in vitro transcription, dideoxy sequencing, single strand rescue with helper phage, and creation of nested deletions in the cloned sequence. (See, e.g., Van Heeke, G. and S.M. Schuster (1989) J. Biol. Chem. 264:5503-5509.) When large quantities of GBAP are needed, e.g. for the production of antibodies, vectors which direct high level expression of GBAP may be used. For example, vectors containing the strong, inducible T5 or T7 bacteriophage promoter may be used.

10 Yeast expression systems may be used for production of GBAP. A number of vectors containing constitutive or inducible promoters, such as alpha factor, alcohol oxidase, and PGH promoters, may be used in the yeast Saccharomyces cerevisiae or Pichia pastoris. In addition, such vectors direct either the secretion or intracellular retention of expressed proteins and enable integration of foreign sequences into the host genome for stable propagation. (See, e.g., Ausubel, 1995, supra;  
15 Bitter, supra; and Scorer, supra.)

Plant systems may also be used for expression of GBAP. Transcription of sequences encoding GBAP may be driven viral promoters, e.g., the 35S and 19S promoters of CaMV used alone or in combination with the omega leader sequence from TMV (Takamatsu, N. (1987) EMBO J. 6:307-311). Alternatively, plant promoters such as the small subunit of RUBISCO or heat shock promoters may be  
20 used. (See, e.g., Coruzzi, supra; Broglie, supra; and Winter, supra.) These constructs can be introduced into plant cells by direct DNA transformation or pathogen-mediated transfection. (See, e.g., The McGraw Hill Yearbook of Science and Technology (1992) McGraw Hill, New York NY, pp. 191-196.)

In mammalian cells, a number of viral-based expression systems may be utilized. In cases  
25 where an adenovirus is used as an expression vector, sequences encoding GBAP may be ligated into an adenovirus transcription/translation complex consisting of the late promoter and tripartite leader sequence. Insertion in a non-essential E1 or E3 region of the viral genome may be used to obtain infective virus which expresses GBAP in host cells. (See, e.g., Logan, J. and T. Shenk (1984) Proc. Natl. Acad. Sci. USA 81:3655-3659.) In addition, transcription enhancers, such as the Rous sarcoma  
30 virus (RSV) enhancer, may be used to increase expression in mammalian host cells. SV40 or EBV-based vectors may also be used for high-level protein expression.

Human artificial chromosomes (HACs) may also be employed to deliver larger fragments of DNA than can be contained in and expressed from a plasmid. HACs of about 6 kb to 10 Mb are constructed and delivered via conventional delivery methods (liposomes, polycationic amino polymers,  
35 or vesicles) for therapeutic purposes. (See, e.g., Harrington, J.J. et al. (1997) Nat. Genet. 15:345-355.)

For long term production of recombinant proteins in mammalian systems, stable expression of GBAP in cell lines is preferred. For example, sequences encoding GBAP can be transformed into cell lines using expression vectors which may contain viral origins of replication and/or endogenous expression elements and a selectable marker gene on the same or on a separate vector. Following the  
5 introduction of the vector, cells may be allowed to grow for about 1 to 2 days in enriched media before being switched to selective media. The purpose of the selectable marker is to confer resistance to a selective agent, and its presence allows growth and recovery of cells which successfully express the introduced sequences. Resistant clones of stably transformed cells may be propagated using tissue culture techniques appropriate to the cell type.

10 Any number of selection systems may be used to recover transformed cell lines. These include, but are not limited to, the herpes simplex virus thymidine kinase and adenine phosphoribosyltransferase genes, for use in *tk* and *apr* cells, respectively. (See, e.g., Wigler, M. et al. (1977) Cell 11:223-232; Lowy, I. et al. (1980) Cell 22:817-823.) Also, antimetabolite, antibiotic, or herbicide resistance can be used as the basis for selection. For example, *dhfr* confers resistance to methotrexate; *neo* confers  
15 resistance to the aminoglycosides neomycin and G-418; and *als* and *pat* confer resistance to chlorsulfuron and phosphinotricin acetyltransferase, respectively. (See, e.g., Wigler, M. et al. (1980) Proc. Natl. Acad. Sci. USA 77:3567-3570; Colbere-Garapin, F. et al. (1981) J. Mol. Biol. 150:1-14.) Additional selectable genes have been described, e.g., *trpB* and *hisD*, which alter cellular requirements for metabolites. (See, e.g., Hartman, S.C. and R.C. Mulligan (1988) Proc. Natl. Acad. Sci. USA  
20 85:8047-8051.) Visible markers, e.g., anthocyanins, green fluorescent proteins (GFP; Clontech),  $\beta$  glucuronidase and its substrate  $\beta$ -glucuronide, or luciferase and its substrate luciferin may be used. These markers can be used not only to identify transformants, but also to quantify the amount of transient or stable protein expression attributable to a specific vector system. (See, e.g., Rhodes, C.A. (1995) Methods Mol. Biol. 55:121-131.)

25 Although the presence/absence of marker gene expression suggests that the gene of interest is also present, the presence and expression of the gene may need to be confirmed. For example, if the sequence encoding GBAP is inserted within a marker gene sequence, transformed cells containing sequences encoding GBAP can be identified by the absence of marker gene function. Alternatively, a marker gene can be placed in tandem with a sequence encoding GBAP under the control of a single  
30 promoter. Expression of the marker gene in response to induction or selection usually indicates expression of the tandem gene as well.

In general, host cells that contain the nucleic acid sequence encoding GBAP and that express GBAP may be identified by a variety of procedures known to those of skill in the art. These procedures include, but are not limited to, DNA-DNA or DNA-RNA hybridizations, PCR amplification, and  
35 protein bioassay or immunoassay techniques which include membrane, solution, or chip based

technologies for the detection and/or quantification of nucleic acid or protein sequences.

Immunological methods for detecting and measuring the expression of GBAP using either specific polyclonal or monoclonal antibodies are known in the art. Examples of such techniques include enzyme-linked immunosorbent assays (ELISAs), radioimmunoassays (RIAs), and fluorescence

5 activated cell sorting (FACS). A two-site, monoclonal-based immunoassay utilizing monoclonal antibodies reactive to two non-interfering epitopes on GBAP is preferred, but a competitive binding assay may be employed. These and other assays are well known in the art. (See, e.g., Hampton, R. et al. (1990) Serological Methods, a Laboratory Manual, APS Press, St. Paul MN, Sect. IV; Coligan, J.E. et al. (1997) Current Protocols in Immunology, Greene Pub. Associates and Wiley-Interscience, New  
10 York NY; and Pound, J.D. (1998) Immunochemical Protocols, Humana Press, Totowa NJ.)

A wide variety of labels and conjugation techniques are known by those skilled in the art and may be used in various nucleic acid and amino acid assays. Means for producing labeled hybridization or PCR probes for detecting sequences related to polynucleotides encoding GBAP include oligolabeling, nick translation, end-labeling, or PCR amplification using a labeled nucleotide. Alternatively, the  
15 sequences encoding GBAP, or any fragments thereof, may be cloned into a vector for the production of an mRNA probe. Such vectors are known in the art, are commercially available, and may be used to synthesize RNA probes in vitro by addition of an appropriate RNA polymerase such as T7, T3, or SP6 and labeled nucleotides. These procedures may be conducted using a variety of commercially available kits, such as those provided by Amersham Pharmacia Biotech, Promega (Madison WI), and US  
20 Biochemical. Suitable reporter molecules or labels which may be used for ease of detection include radionuclides, enzymes, fluorescent, chemiluminescent, or chromogenic agents, as well as substrates, cofactors, inhibitors, magnetic particles, and the like.

Host cells transformed with nucleotide sequences encoding GBAP may be cultured under conditions suitable for the expression and recovery of the protein from cell culture. The protein  
25 produced by a transformed cell may be secreted or retained intracellularly depending on the sequence and/or the vector used. As will be understood by those of skill in the art, expression vectors containing polynucleotides which encode GBAP may be designed to contain signal sequences which direct secretion of GBAP through a prokaryotic or eukaryotic cell membrane.

In addition, a host cell strain may be chosen for its ability to modulate expression of the  
30 inserted sequences or to process the expressed protein in the desired fashion. Such modifications of the polypeptide include, but are not limited to, acetylation, carboxylation, glycosylation, phosphorylation, lipidation, and acylation. Post-translational processing which cleaves a "prepro" or "pro" form of the protein may also be used to specify protein targeting, folding, and/or activity. Different host cells which have specific cellular machinery and characteristic mechanisms for post-translational activities  
35 (e.g., CHO, HeLa, MDCK, HEK293, and WI38) are available from the American Type Culture



Collection (ATCC, Manassas VA) and may be chosen to ensure the correct modification and processing of the foreign protein.

In another embodiment of the invention, natural, modified, or recombinant nucleic acid sequences encoding GBAP may be ligated to a heterologous sequence resulting in translation of a fusion protein in any of the aforementioned host systems. For example, a chimeric GBAP protein containing a heterologous moiety that can be recognized by a commercially available antibody may facilitate the screening of peptide libraries for inhibitors of GBAP activity. Heterologous protein and peptide moieties may also facilitate purification of fusion proteins using commercially available affinity matrices. Such moieties include, but are not limited to, glutathione S-transferase (GST), maltose binding protein (MBP), thioredoxin (Trx), calmodulin binding peptide (CBP), 6-His, FLAG, *c-myc*, and hemagglutinin (HA). GST, MBP, Trx, CBP, and 6-His enable purification of their cognate fusion proteins on immobilized glutathione, maltose, phenylarsine oxide, calmodulin, and metal-chelate resins, respectively. FLAG, *c-myc*, and hemagglutinin (HA) enable immunoaffinity purification of fusion proteins using commercially available monoclonal and polyclonal antibodies that specifically recognize these epitope tags. A fusion protein may also be engineered to contain a proteolytic cleavage site located between the GBAP encoding sequence and the heterologous protein sequence, so that GBAP may be cleaved away from the heterologous moiety following purification. Methods for fusion protein expression and purification are discussed in Ausubel (1995, supra, ch. 10). A variety of commercially available kits may also be used to facilitate expression and purification of fusion proteins.

In a further embodiment of the invention, synthesis of radiolabeled GBAP may be achieved in vitro using the TNT rabbit reticulocyte lysate or wheat germ extract system (Promega). These systems couple transcription and translation of protein-coding sequences operably associated with the T7, T3, or SP6 promoters. Translation takes place in the presence of a radiolabeled amino acid precursor, for example, <sup>35</sup>S-methionine.

GBAP of the present invention or fragments thereof may be used to screen for compounds that specifically bind to GBAP. At least one and up to a plurality of test compounds may be screened for specific binding to GBAP. Examples of test compounds include antibodies, oligonucleotides, proteins (e.g., receptors), or small molecules.

In one embodiment, the compound thus identified is closely related to the natural ligand of GBAP, e.g., a ligand or fragment thereof, a natural substrate, a structural or functional mimetic, or a natural binding partner. (See, Coligan, J.E. et al. (1991) Current Protocols in Immunology 1(2): Chapter 5.) Similarly, the compound can be closely related to the natural receptor to which GBAP binds, or to at least a fragment of the receptor, e.g., the ligand binding site. In either case, the compound can be rationally designed using known techniques. In one embodiment, screening for these compounds involves producing appropriate cells which express GBAP, either as a secreted

protein or on the cell membrane. Preferred cells include cells from mammals, yeast, Drosophila, or E. coli. Cells expressing GBAP or cell membrane fractions which contain GBAP are then contacted with a test compound and binding, stimulation, or inhibition of activity of either GBAP or the compound is analyzed.

5 An assay may simply test binding of a test compound to the polypeptide, wherein binding is detected by a fluorophore, radioisotope, enzyme conjugate, or other detectable label. For example, the assay may comprise the steps of combining at least one test compound with GBAP, either in solution or affixed to a solid support, and detecting the binding of GBAP to the compound.

Alternatively, the assay may detect or measure binding of a test compound in the presence of a  
10 labeled competitor. Additionally, the assay may be carried out using cell-free preparations, chemical libraries, or natural product mixtures, and the test compound(s) may be free in solution or affixed to a solid support.

GBAP of the present invention or fragments thereof may be used to screen for compounds that modulate the activity of GBAP. Such compounds may include agonists, antagonists, or partial or  
15 inverse agonists. In one embodiment, an assay is performed under conditions permissive for GBAP activity, wherein GBAP is combined with at least one test compound, and the activity of GBAP in the presence of a test compound is compared with the activity of GBAP in the absence of the test compound. A change in the activity of GBAP in the presence of the test compound is indicative of a compound that modulates the activity of GBAP. Alternatively, a test compound is combined with an  
20 in vitro or cell-free system comprising GBAP under conditions suitable for GBAP activity, and the assay is performed. In either of these assays, a test compound which modulates the activity of GBAP may do so indirectly and need not come in direct contact with the test compound. At least one and up to a plurality of test compounds may be screened.

In another embodiment, polynucleotides encoding GBAP or their mammalian homologs may  
25 be "knocked out" in an animal model system using homologous recombination in embryonic stem (ES) cells. Such techniques are well known in the art and are useful for the generation of animal models of human disease. (See, e.g., U.S. Patent No. 5,175,383 and U.S. Patent No. 5,767,337.) For example, mouse ES cells, such as the mouse 129/SvJ cell line, are derived from the early mouse embryo and grown in culture. The ES cells are transformed with a vector containing the gene of  
30 interest disrupted by a marker gene, e.g., the neomycin phosphotransferase gene (neo; Capecchi, M.R. (1989) Science 244:1288-1292). The vector integrates into the corresponding region of the host genome by homologous recombination. Alternatively, homologous recombination takes place using the Cre-loxP system to knockout a gene of interest in a tissue- or developmental stage-specific manner (Marth, J.D. (1996) Clin. Invest. 97:1999-2002; Wagner, K.U. et al. (1997) Nucleic Acids  
35 Res. 25:4323-4330). Transformed ES cells are identified and microinjected into mouse cell blastocysts such as those from the C57BL/6 mouse strain. The blastocysts are surgically transferred

to pseudopregnant dams, and the resulting chimeric progeny are genotyped and bred to produce heterozygous or homozygous strains. Transgenic animals thus generated may be tested with potential therapeutic or toxic agents.

Polynucleotides encoding GBAP may also be manipulated in vitro in ES cells derived from human blastocysts. Human ES cells have the potential to differentiate into at least eight separate cell lineages including endoderm, mesoderm, and ectodermal cell types. These cell lineages differentiate into, for example, neural cells, hematopoietic lineages, and cardiomyocytes (Thomson, J.A. et al. (1998) Science 282:1145-1147).

Polynucleotides encoding GBAP can also be used to create "knockin" humanized animals (pigs) or transgenic animals (mice or rats) to model human disease. With knockin technology, a region of a polynucleotide encoding GBAP is injected into animal ES cells, and the injected sequence integrates into the animal cell genome. Transformed cells are injected into blastulae, and the blastulae are implanted as described above. Transgenic progeny or inbred lines are studied and treated with potential pharmaceutical agents to obtain information on treatment of a human disease. Alternatively, a mammal inbred to overexpress GBAP, e.g., by secreting GBAP in its milk, may also serve as a convenient source of that protein (Janne, J. et al. (1998) Biotechnol. Annu. Rev. 4:55-74).

#### THERAPEUTICS

Chemical and structural similarity, e.g., in the context of sequences and motifs, exists between regions of GBAP and GTP-binding associated proteins. In addition, the expression of GBAP is closely associated with reproductive tissues, inflammation and the immune response, trauma, cell proliferation, and cancer. Therefore, GBAP appears to play a role in immune system, reproductive, nervous system, and cell signaling disorders, and cell proliferative disorders including cancer. In the treatment of disorders associated with increased GBAP expression or activity, it is desirable to decrease the expression or activity of GBAP. In the treatment of disorders associated with decreased GBAP expression or activity, it is desirable to increase the expression or activity of GBAP.

Therefore, in one embodiment, GBAP or a fragment or derivative thereof may be administered to a subject to treat or prevent a disorder associated with decreased expression or activity of GBAP. Examples of such disorders include, but are not limited to, an immune system disorder such as inflammation, actinic keratosis, acquired immunodeficiency syndrome (AIDS), Addison's disease, adult respiratory distress syndrome, allergies, ankylosing spondylitis, amyloidosis, anemia, arteriosclerosis, asthma, atherosclerosis, autoimmune hemolytic anemia, autoimmune thyroiditis, bronchitis, bursitis, cholecystitis, cirrhosis, contact dermatitis, Crohn's disease, atopic dermatitis, dermatomyositis, diabetes mellitus, emphysema, erythroblastosis fetalis, erythema nodosum, atrophic gastritis, glomerulonephritis, Goodpasture's syndrome, gout, Graves' disease, Hashimoto's thyroiditis, paroxysmal nocturnal hemoglobinuria, hepatitis, hypereosinophilia, irritable

bowel syndrome, episodic lymphopenia with lymphocytotoxins, mixed connective tissue disease (MCTD), multiple sclerosis, myasthenia gravis, myocardial or pericardial inflammation, myelofibrosis, osteoarthritis, osteoporosis, pancreatitis, polycythemia vera, polymyositis, psoriasis, Reiter's syndrome, rheumatoid arthritis, scleroderma, Sjögren's syndrome, systemic anaphylaxis, 5 systemic lupus erythematosus, systemic sclerosis, primary thrombocythemia, thrombocytopenic purpura, ulcerative colitis, uveitis, Werner syndrome, complications of cancer, hemodialysis, and extracorporeal circulation, trauma, and hematopoietic cancer including lymphoma, leukemia, and myeloma; a reproductive disorder such as a disorder of prolactin production, infertility, including tubal disease, ovulatory defects, and endometriosis, a disruption of the estrous cycle, a disruption of 10 the menstrual cycle, polycystic ovary syndrome, ovarian hyperstimulation syndrome, an endometrial or ovarian tumor, a uterine fibroid, autoimmune disorders, an ectopic pregnancy, and teratogenesis, cancer of the breast, fibrocystic breast disease, and galactorrhea, a disruption of spermatogenesis, abnormal sperm physiology, cancer of the testis, cancer of the prostate, benign prostatic hyperplasia, prostatitis, Peyronie's disease, impotence, carcinoma of the male breast, and gynecomastia; a nervous 15 system disorder such as epilepsy, ischemic cerebrovascular disease, stroke, cerebral neoplasms, Alzheimer's disease, Pick's disease, Huntington's disease, dementia, Parkinson's disease and other extrapyramidal disorders, amyotrophic lateral sclerosis and other motor neuron disorders, progressive neural muscular atrophy, retinitis pigmentosa, hereditary ataxias, multiple sclerosis and other demyelinating diseases, bacterial and viral meningitis, brain abscess, subdural empyema, epidural 20 abscess, suppurative intracranial thrombophlebitis, myelitis and radiculitis, viral central nervous system disease, prion diseases including kuru, Creutzfeldt-Jakob disease, and Gerstmann-Straussler-Scheinker syndrome, fatal familial insomnia, nutritional and metabolic diseases of the nervous system, neurofibromatosis, tuberous sclerosis, cerebelloretinal hemangioblastomatosis, encephalotrigeminal syndrome, mental retardation and other developmental disorders of the central 25 nervous system, cerebral palsy, neuroskeletal disorders, autonomic nervous system disorders, cranial nerve disorders, spinal cord diseases, muscular dystrophy and other neuromuscular disorders, peripheral nervous system disorders, dermatomyositis and polymyositis, inherited, metabolic, endocrine, and toxic myopathies, myasthenia gravis, periodic paralysis, mental disorders including mood, anxiety, and schizophrenic disorders, akathisia, amnesia, catatonia, diabetic neuropathy, 30 tardive dyskinesia, dystonias, paranoid psychoses, postherpetic neuralgia, and Tourette's disorder; a cell signaling disorder including endocrine disorders such as disorders of the hypothalamus and pituitary resulting from lesions such as primary brain tumors, adenomas, infarction associated with pregnancy, hypophysectomy, aneurysms, vascular malformations, thrombosis, infections, immunological disorders, and complications due to head trauma; disorders associated with 35 hyperpituitarism including acromegaly, gigantism, and syndrome of inappropriate antidiuretic hormone (ADH) secretion (SIADH) often caused by benign adenoma; disorders associated with

hypothyroidism including goiter, myxedema, acute thyroiditis associated with bacterial infection; disorders associated with hyperparathyroidism including Conn disease (chronic hypercalcemia); pancreatic disorders such as Type I or Type II diabetes mellitus and associated complications; disorders associated with the adrenals such as hyperplasia, carcinoma, or adenoma of the adrenal cortex, hypertension associated with alkalosis; disorders associated with gonadal steroid hormones such as: in women, abnormal prolactin production, infertility, endometriosis, perturbations of the menstrual cycle, polycystic ovarian disease, hyperprolactinemia, isolated gonadotropin deficiency, amenorrhea, galactorrhea, hermaphroditism, hirsutism and virilization, breast cancer, and, in post-menopausal women, osteoporosis; and, in men, Leydig cell deficiency, male climacteric phase, and germinal cell aplasia, hypergonadal disorders associated with Leydig cell tumors, androgen resistance associated with absence of androgen receptors, syndrome of 5  $\alpha$ -reductase, and gynecomastia; and a cell proliferative disorder such as actinic keratosis, arteriosclerosis, atherosclerosis, bursitis, cirrhosis, hepatitis, mixed connective tissue disease (MCTD), myelofibrosis, paroxysmal nocturnal hemoglobinuria, polycythemia vera, psoriasis, primary thrombocythemia, and cancers including adenocarcinoma, leukemia, lymphoma, melanoma, myeloma, sarcoma, teratocarcinoma, and, in particular, cancers of the adrenal gland, bladder, bone, bone marrow, brain, breast, cervix, gall bladder, ganglia, gastrointestinal tract, heart, kidney, liver, lung, muscle, ovary, pancreas, parathyroid, penis, prostate, salivary glands, skin, spleen, testis, thymus, thyroid, and uterus.

In another embodiment, a vector capable of expressing GBAP or a fragment or derivative thereof may be administered to a subject to treat or prevent a disorder associated with decreased expression or activity of GBAP including, but not limited to, those described above.

In a further embodiment, a pharmaceutical composition comprising a substantially purified GBAP in conjunction with a suitable pharmaceutical carrier may be administered to a subject to treat or prevent a disorder associated with decreased expression or activity of GBAP including, but not limited to, those provided above.

In still another embodiment, an agonist which modulates the activity of GBAP may be administered to a subject to treat or prevent a disorder associated with decreased expression or activity of GBAP including, but not limited to, those listed above.

In a further embodiment, an antagonist of GBAP may be administered to a subject to treat or prevent a disorder associated with increased expression or activity of GBAP. Examples of such disorders include, but are not limited to, those immune system, reproductive, nervous system, and cell signaling disorders, and cell proliferative disorders including cancer, described above. In one aspect, an antibody which specifically binds GBAP may be used directly as an antagonist or indirectly as a targeting or delivery mechanism for bringing a pharmaceutical agent to cells or tissues which express GBAP.

In an additional embodiment, a vector expressing the complement of the polynucleotide encoding GBAP may be administered to a subject to treat or prevent a disorder associated with increased expression or activity of GBAP including, but not limited to, those described above.

In other embodiments, any of the proteins, antagonists, antibodies, agonists, complementary sequences, or vectors of the invention may be administered in combination with other appropriate therapeutic agents. Selection of the appropriate agents for use in combination therapy may be made by one of ordinary skill in the art, according to conventional pharmaceutical principles. The combination of therapeutic agents may act synergistically to effect the treatment or prevention of the various disorders described above. Using this approach, one may be able to achieve therapeutic efficacy with lower dosages of each agent, thus reducing the potential for adverse side effects.

An antagonist of GBAP may be produced using methods which are generally known in the art. In particular, purified GBAP may be used to produce antibodies or to screen libraries of pharmaceutical agents to identify those which specifically bind GBAP. Antibodies to GBAP may also be generated using methods that are well known in the art. Such antibodies may include, but are not limited to, polyclonal, monoclonal, chimeric, and single chain antibodies, Fab fragments, and fragments produced by a Fab expression library. Neutralizing antibodies (i.e., those which inhibit dimer formation) are generally preferred for therapeutic use.

For the production of antibodies, various hosts including goats, rabbits, rats, mice, humans, and others may be immunized by injection with GBAP or with any fragment or oligopeptide thereof which has immunogenic properties. Depending on the host species, various adjuvants may be used to increase immunological response. Such adjuvants include, but are not limited to, Freund's, mineral gels such as aluminum hydroxide, and surface active substances such as lysolecithin, pluronic polyols, polyanions, peptides, oil emulsions, KLH, and dinitrophenol. Among adjuvants used in humans, BCG (bacilli Calmette-Guerin) and Corynebacterium parvum are especially preferable.

It is preferred that the oligopeptides, peptides, or fragments used to induce antibodies to GBAP have an amino acid sequence consisting of at least about 5 amino acids, and generally will consist of at least about 10 amino acids. It is also preferable that these oligopeptides, peptides, or fragments are identical to a portion of the amino acid sequence of the natural protein. Short stretches of GBAP amino acids may be fused with those of another protein, such as KLH, and antibodies to the chimeric molecule may be produced.

Monoclonal antibodies to GBAP may be prepared using any technique which provides for the production of antibody molecules by continuous cell lines in culture. These include, but are not limited to, the hybridoma technique, the human B-cell hybridoma technique, and the EBV-hybridoma technique. (See, e.g., Kohler, G. et al. (1975) Nature 256:495-497; Kozbor, D. et al. (1985) J. Immunol. Methods 81:31-42; Cote, R.J. et al. (1983) Proc. Natl. Acad. Sci. USA 80:2026-2030; and

Cole, S.P. et al. (1984) Mol. Cell Biol. 62:109-120.)

In addition, techniques developed for the production of "chimeric antibodies," such as the splicing of mouse antibody genes to human antibody genes to obtain a molecule with appropriate antigen specificity and biological activity, can be used. (See, e.g., Morrison, S.L. et al. (1984) Proc. Natl. Acad. Sci. USA 81:6851-6855; Neuberger, M.S. et al. (1984) Nature 312:604-608; and Takeda, S. et al. (1985) Nature 314:452-454.) Alternatively, techniques described for the production of single chain antibodies may be adapted, using methods known in the art, to produce GBAP-specific single chain antibodies. Antibodies with related specificity, but of distinct idiotypic composition, may be generated by chain shuffling from random combinatorial immunoglobulin libraries. (See, e.g., Burton, D.R. (1991) Proc. Natl. Acad. Sci. USA 88:10134-10137.)

Antibodies may also be produced by inducing *in vivo* production in the lymphocyte population or by screening immunoglobulin libraries or panels of highly specific binding reagents as disclosed in the literature. (See, e.g., Orlandi, R. et al. (1989) Proc. Natl. Acad. Sci. USA 86:3833-3837; Winter, G. et al. (1991) Nature 349:293-299.)

Antibody fragments which contain specific binding sites for GBAP may also be generated. For example, such fragments include, but are not limited to, F(ab')<sub>2</sub> fragments produced by pepsin digestion of the antibody molecule and Fab fragments generated by reducing the disulfide bridges of the F(ab')<sub>2</sub> fragments. Alternatively, Fab expression libraries may be constructed to allow rapid and easy identification of monoclonal Fab fragments with the desired specificity. (See, e.g., Huse, W.D. et al. (1989) Science 246:1275-1281.)

Various immunoassays may be used for screening to identify antibodies having the desired specificity. Numerous protocols for competitive binding or immunoradiometric assays using either polyclonal or monoclonal antibodies with established specificities are well known in the art. Such immunoassays typically involve the measurement of complex formation between GBAP and its specific antibody. A two-site, monoclonal-based immunoassay utilizing monoclonal antibodies reactive to two non-interfering GBAP epitopes is generally used, but a competitive binding assay may also be employed (Pound, *supra*).

Various methods such as Scatchard analysis in conjunction with radioimmunoassay techniques may be used to assess the affinity of antibodies for GBAP. Affinity is expressed as an association constant,  $K_a$ , which is defined as the molar concentration of GBAP-antibody complex divided by the molar concentrations of free antigen and free antibody under equilibrium conditions. The  $K_a$  determined for a preparation of polyclonal antibodies, which are heterogeneous in their affinities for multiple GBAP epitopes, represents the average affinity, or avidity, of the antibodies for GBAP. The  $K_a$  determined for a preparation of monoclonal antibodies, which are monospecific for a particular GBAP epitope, represents a true measure of affinity. High-affinity antibody preparations with  $K_a$  ranging from

about  $10^9$  to  $10^{12}$  L/mole are preferred for use in immunoassays in which the GBAP-antibody complex must withstand rigorous manipulations. Low-affinity antibody preparations with  $K_a$  ranging from about  $10^6$  to  $10^7$  L/mole are preferred for use in immunopurification and similar procedures which ultimately require dissociation of GBAP, preferably in active form, from the antibody (Catty, D. (1988)

- 5 Antibodies, Volume I: A Practical Approach, IRL Press, Washington DC; Liddell, J.E. and A. Cryer (1991) A Practical Guide to Monoclonal Antibodies, John Wiley & Sons, New York NY).

The titer and avidity of polyclonal antibody preparations may be further evaluated to determine the quality and suitability of such preparations for certain downstream applications. For example, a polyclonal antibody preparation containing at least 1-2 mg specific antibody/ml, preferably 5-10 mg  
10 specific antibody/ml, is generally employed in procedures requiring precipitation of GBAP-antibody complexes. Procedures for evaluating antibody specificity, titer, and avidity, and guidelines for antibody quality and usage in various applications, are generally available. (See, e.g., Catty, supra, and Coligan et al., supra.)

In another embodiment of the invention, the polynucleotides encoding GBAP, or any fragment  
15 or complement thereof, may be used for therapeutic purposes. In one aspect, modifications of gene expression can be achieved by designing complementary sequences or antisense molecules (DNA, RNA, PNA, or modified oligonucleotides) to the coding or regulatory regions of the gene encoding GBAP. Such technology is well known in the art, and antisense oligonucleotides or larger fragments can be designed from various locations along the coding or control regions of sequences encoding GBAP.  
20 (See, e.g., Agrawal, S., ed. (1996) Antisense Therapeutics, Humana Press Inc., Totawa NJ.)

In therapeutic use, any gene delivery system suitable for introduction of the antisense sequences into appropriate target cells can be used. Antisense sequences can be delivered intracellularly in the form of an expression plasmid which, upon transcription, produces a sequence complementary to at least a portion of the cellular sequence encoding the target protein. (See, e.g.,  
25 Slater, J.E. et al. (1998) *J. Allergy Clin. Immunol.* 102(3):469-475; and Scanlon, K.J. et al. (1995) 9(13):1288-1296.) Antisense sequences can also be introduced intracellularly through the use of viral vectors, such as retrovirus and adeno-associated virus vectors. (See, e.g., Miller, A.D. (1990) *Blood* 76:271; Ausubel, supra; Uckert, W. and W. Walther (1994) *Pharmacol. Ther.* 63(3):323-347.) Other gene delivery mechanisms include liposome-derived systems, artificial viral envelopes, and other  
30 systems known in the art. (See, e.g., Rossi, J.J. (1995) *Br. Med. Bull.* 51(1):217-225; Boado, R.J. et al. (1998) *J. Pharm. Sci.* 87(11):1308-1315; and Morris, M.C. et al. (1997) *Nucleic Acids Res.* 25(14):2730-2736.)

In another embodiment of the invention, polynucleotides encoding GBAP may be used for somatic or germline gene therapy. Gene therapy may be performed to (i) correct a genetic deficiency  
35 (e.g., in the cases of severe combined immunodeficiency (SCID)-X1 disease characterized by X-linked



inheritance (Cavazzana-Calvo, M. et al. (2000) Science 288:669-672), severe combined immunodeficiency syndrome associated with an inherited adenosine deaminase (ADA) deficiency (Blaese, R.M. et al. (1995) Science 270:475-480; Bordignon, C. et al. (1995) Science 270:470-475), cystic fibrosis (Zabner, J. et al. (1993) Cell 75:207-216; Crystal, R.G. et al. (1995) Hum. Gene Therapy 6:643-666; Crystal, R.G. et al. (1995) Hum. Gene Therapy 6:667-703), thalassemias, familial hypercholesterolemia, and hemophilia resulting from Factor VIII or Factor IX deficiencies (Crystal, R.G. (1995) Science 270:404-410; Verma, I.M. and Somia, N. (1997) Nature 389:239-242)), (ii) express a conditionally lethal gene product (e.g., in the case of cancers which result from unregulated cell proliferation), or (iii) express a protein which affords protection against intracellular parasites (e.g., against human retroviruses, such as human immunodeficiency virus (HIV) (Baltimore, D. (1988) Nature 335:395-396; Poeschla, E. et al. (1996) Proc. Natl. Acad. Sci. USA. 93:11395-11399), hepatitis B or C virus (HBV, HCV); fungal parasites, such as Candida albicans and Paracoccidioides brasiliensis; and protozoan parasites such as Plasmodium falciparum and Trypanosoma cruzi). In the case where a genetic deficiency in GBAP expression or regulation causes disease, the expression of GBAP from an appropriate population of transduced cells may alleviate the clinical manifestations caused by the genetic deficiency.

In a further embodiment of the invention, diseases or disorders caused by deficiencies in GBAP are treated by constructing mammalian expression vectors encoding GBAP and introducing these vectors by mechanical means into GBAP-deficient cells. Mechanical transfer technologies for use with cells in vivo or ex vitro include (i) direct DNA microinjection into individual cells, (ii) ballistic gold particle delivery, (iii) liposome-mediated transfection, (iv) receptor-mediated gene transfer, and (v) the use of DNA transposons (Morgan, R.A. and W.F. Anderson (1993) Annu. Rev. Biochem. 62:191-217; Ivics, Z. (1997) Cell 91:501-510; Boulay, J-L. and H. Récipon (1998) Curr. Opin. Biotechnol. 9:445-450).

Expression vectors that may be effective for the expression of GBAP include, but are not limited to, the PCDNA 3.1, EPITAG, PRCCMV2, PREP, PVAX vectors (Invitrogen, Carlsbad CA), PCMV-SCRIPT, PCMV-TAG, PEGSH/PERV (Stratagene, La Jolla CA), and PTET-OFF, PTET-ON, PTRE2, PTRE2-LUC, PTK-HYG (Clontech, Palo Alto CA). GBAP may be expressed using (i) a constitutively active promoter, (e.g., from cytomegalovirus (CMV), Rous sarcoma virus (RSV), SV40 virus, thymidine kinase (TK), or  $\beta$ -actin genes), (ii) an inducible promoter (e.g., the tetracycline-regulated promoter (Gossen, M. and H. Bujard (1992) Proc. Natl. Acad. Sci. USA 89:5547-5551; Gossen, M. et al. (1995) Science 268:1766-1769; Rossi, F.M.V. and H.M. Blau (1998) Curr. Opin. Biotechnol. 9:451-456), commercially available in the T-REX plasmid (Invitrogen)); the ecdysone-inducible promoter (available in the plasmids PVGRXR and PIND; Invitrogen); the FK506/rapamycin inducible promoter; or the RU486/mifepristone inducible promoter (Rossi, F.M.V.

and H.M. Blau, *supra*)), or (iii) a tissue-specific promoter or the native promoter of the endogenous gene encoding GBAP from a normal individual.

Commercially available liposome transformation kits (e.g., the PERFECT LIPID TRANSFECTION KIT, available from Invitrogen) allow one with ordinary skill in the art to deliver  
5 polynucleotides to target cells in culture and require minimal effort to optimize experimental parameters. In the alternative, transformation is performed using the calcium phosphate method (Graham, F.L. and A.J. Eb (1973) *Virology* 52:456-467), or by electroporation (Neumann, E. et al. (1982) *EMBO J.* 1:841-845). The introduction of DNA to primary cells requires modification of these standardized mammalian transfection protocols.

10 In another embodiment of the invention, diseases or disorders caused by genetic defects with respect to GBAP expression are treated by constructing a retrovirus vector consisting of (i) the polynucleotide encoding GBAP under the control of an independent promoter or the retrovirus long terminal repeat (LTR) promoter, (ii) appropriate RNA packaging signals, and (iii) a Rev-responsive element (RRE) along with additional retrovirus *cis*-acting RNA sequences and coding sequences  
15 required for efficient vector propagation. Retrovirus vectors (e.g., PFB and PFBNEO) are commercially available (Stratagene) and are based on published data (Riviere, I. et al. (1995) *Proc. Natl. Acad. Sci. USA* 92:6733-6737), incorporated by reference herein. The vector is propagated in an appropriate vector producing cell line (VPCL) that expresses an envelope gene with a tropism for receptors on the target cells or a promiscuous envelope protein such as VSVg (Armentano, D. et al.  
20 (1987) *J. Virol.* 61:1647-1650; Bender, M.A. et al. (1987) *J. Virol.* 61:1639-1646; Adam, M.A. and A.D. Miller (1988) *J. Virol.* 62:3802-3806; Dull, T. et al. (1998) *J. Virol.* 72:8463-8471; Zufferey, R. et al. (1998) *J. Virol.* 72:9873-9880). U.S. Patent Number 5,910,434 to Rigg ("Method for obtaining retrovirus packaging cell lines producing high transducing efficiency retroviral supernatant") discloses a method for obtaining retrovirus packaging cell lines and is hereby incorporated by reference.

25 Propagation of retrovirus vectors, transduction of a population of cells (e.g., CD4<sup>+</sup> T-cells), and the return of transduced cells to a patient are procedures well known to persons skilled in the art of gene therapy and have been well documented (Ranga, U. et al. (1997) *J. Virol.* 71:7020-7029; Bauer, G. et al. (1997) *Blood* 89:2259-2267; Bonyhadi, M.L. (1997) *J. Virol.* 71:4707-4716; Ranga, U. et al. (1998) *Proc. Natl. Acad. Sci. USA* 95:1201-1206; Su, L. (1997) *Blood* 89:2283-2290).

30 In the alternative, an adenovirus-based gene therapy delivery system is used to deliver polynucleotides encoding GBAP to cells which have one or more genetic abnormalities with respect to the expression of GBAP. The construction and packaging of adenovirus-based vectors are well known to those with ordinary skill in the art. Replication defective adenovirus vectors have proven to be versatile for importing genes encoding immunoregulatory proteins into intact islets in the pancreas  
35 (Csete, M.E. et al. (1995) *Transplantation* 27:263-268). Potentially useful adenoviral vectors are

described in U.S. Patent Number 5,707,618 to Armentano ("Adenovirus vectors for gene therapy"), hereby incorporated by reference. For adenoviral vectors, see also Antinozzi, P.A. et al. (1999) *Annu. Rev. Nutr.* 19:511-544; and Verma, I.M. and N. Somia (1997) *Nature* 18:389:239-242, both incorporated by reference herein.

5 In another alternative, a herpes-based, gene therapy delivery system is used to deliver polynucleotides encoding GBAP to target cells which have one or more genetic abnormalities with respect to the expression of GBAP. The use of herpes simplex virus (HSV)-based vectors may be especially valuable for introducing GBAP to cells of the central nervous system, for which HSV has a tropism. The construction and packaging of herpes-based vectors are well known to those with  
10 ordinary skill in the art. A replication-competent herpes simplex virus (HSV) type 1-based vector has been used to deliver a reporter gene to the eyes of primates (Liu, X. et al. (1999) *Exp. Eye Res.* 169:385-395). The construction of a HSV-1 virus vector has also been disclosed in detail in U.S. Patent Number 5,804,413 to DeLuca ("Herpes simplex virus strains for gene transfer"), which is hereby incorporated by reference. U.S. Patent Number 5,804,413 teaches the use of recombinant HSV  
15 d92 which consists of a genome containing at least one exogenous gene to be transferred to a cell under the control of the appropriate promoter for purposes including human gene therapy. Also taught by this patent are the construction and use of recombinant HSV strains deleted for ICP4, ICP27 and ICP22. For HSV vectors, see also Goins, W.F. et al. (1999) *J. Virol.* 73:519-532 and Xu, H. et al. (1994) *Dev. Biol.* 163:152-161, hereby incorporated by reference. The manipulation of cloned herpesvirus  
20 sequences, the generation of recombinant virus following the transfection of multiple plasmids containing different segments of the large herpesvirus genomes, the growth and propagation of herpesvirus, and the infection of cells with herpesvirus are techniques well known to those of ordinary skill in the art.

In another alternative, an alphavirus (positive, single-stranded RNA virus) vector is used to  
25 deliver polynucleotides encoding GBAP to target cells. The biology of the prototypic alphavirus, Semliki Forest Virus (SFV), has been studied extensively and gene transfer vectors have been based on the SFV genome (Garoff, H. and K.-J. Li (1998) *Curr. Opin. Biotech.* 9:464-469). During alphavirus RNA replication, a subgenomic RNA is generated that normally encodes the viral capsid proteins. This subgenomic RNA replicates to higher levels than the full-length genomic RNA, resulting in the  
30 overproduction of capsid proteins relative to the viral proteins with enzymatic activity (e.g., protease and polymerase). Similarly, inserting the coding sequence for GBAP into the alphavirus genome in place of the capsid-coding region results in the production of a large number of GBAP-coding RNAs and the synthesis of high levels of GBAP in vector transduced cells. While alphavirus infection is typically associated with cell lysis within a few days, the ability to establish a persistent infection in  
35 hamster normal kidney cells (BHK-21) with a variant of Sindbis virus (SIN) indicates that the lytic

replication of alphaviruses can be altered to suit the needs of the gene therapy application (Dryga, S.A. et al. (1997) Virology 228:74-83). The wide host range of alphaviruses will allow the introduction of GBAP into a variety of cell types. The specific transduction of a subset of cells in a population may require the sorting of cells prior to transduction. The methods of manipulating infectious cDNA clones of alphaviruses, performing alphavirus cDNA and RNA transfections, and performing alphavirus infections, are well known to those with ordinary skill in the art.

Oligonucleotides derived from the transcription initiation site, e.g., between about positions -10 and +10 from the start site, may also be employed to inhibit gene expression. Similarly, inhibition can be achieved using triple helix base-pairing methodology. Triple helix pairing is useful because it causes inhibition of the ability of the double helix to open sufficiently for the binding of polymerases, transcription factors, or regulatory molecules. Recent therapeutic advances using triplex DNA have been described in the literature. (See, e.g., Gee, J.E. et al. (1994) in Huber, B.E. and B.I. Carr, Molecular and Immunologic Approaches, Futura Publishing, Mt. Kisco NY, pp. 163-177.) A complementary sequence or antisense molecule may also be designed to block translation of mRNA by preventing the transcript from binding to ribosomes.

Ribozymes, enzymatic RNA molecules, may also be used to catalyze the specific cleavage of RNA. The mechanism of ribozyme action involves sequence-specific hybridization of the ribozyme molecule to complementary target RNA, followed by endonucleolytic cleavage. For example, engineered hammerhead motif ribozyme molecules may specifically and efficiently catalyze endonucleolytic cleavage of sequences encoding GBAP.

Specific ribozyme cleavage sites within any potential RNA target are initially identified by scanning the target molecule for ribozyme cleavage sites, including the following sequences: GUA, GUU, and GUC. Once identified, short RNA sequences of between 15 and 20 ribonucleotides, corresponding to the region of the target gene containing the cleavage site, may be evaluated for secondary structural features which may render the oligonucleotide inoperable. The suitability of candidate targets may also be evaluated by testing accessibility to hybridization with complementary oligonucleotides using ribonuclease protection assays.

Complementary ribonucleic acid molecules and ribozymes of the invention may be prepared by any method known in the art for the synthesis of nucleic acid molecules. These include techniques for chemically synthesizing oligonucleotides such as solid phase phosphoramidite chemical synthesis. Alternatively, RNA molecules may be generated by in vitro and in vivo transcription of DNA sequences encoding GBAP. Such DNA sequences may be incorporated into a wide variety of vectors with suitable RNA polymerase promoters such as T7 or SP6. Alternatively, these cDNA constructs that synthesize complementary RNA, constitutively or inducibly, can be introduced into cell lines, cells, or tissues.

RNA molecules may be modified to increase intracellular stability and half-life. Possible modifications include, but are not limited to, the addition of flanking sequences at the 5' and/or 3' ends of the molecule, or the use of phosphorothioate or 2' O-methyl rather than phosphodiesterase linkages within the backbone of the molecule. This concept is inherent in the production of PNAs and can be extended in all of these molecules by the inclusion of nontraditional bases such as inosine, queosine, and wybutosine, as well as acetyl-, methyl-, thio-, and similarly modified forms of adenine, cytidine, guanine, thymine, and uridine which are not as easily recognized by endogenous endonucleases.

An additional embodiment of the invention encompasses a method for screening for a compound which is effective in altering expression of a polynucleotide encoding GBAP. Compounds which may be effective in altering expression of a specific polynucleotide may include, but are not limited to, oligonucleotides, antisense oligonucleotides, triple helix-forming oligonucleotides, transcription factors and other polypeptide transcriptional regulators, and non-macromolecular chemical entities which are capable of interacting with specific polynucleotide sequences. Effective compounds may alter polynucleotide expression by acting as either inhibitors or promoters of polynucleotide expression. Thus, in the treatment of disorders associated with increased GBAP expression or activity, a compound which specifically inhibits expression of the polynucleotide encoding GBAP may be therapeutically useful, and in the treatment of disorders associated with decreased GBAP expression or activity, a compound which specifically promotes expression of the polynucleotide encoding GBAP may be therapeutically useful.

At least one, and up to a plurality, of test compounds may be screened for effectiveness in altering expression of a specific polynucleotide. A test compound may be obtained by any method commonly known in the art, including chemical modification of a compound known to be effective in altering polynucleotide expression; selection from an existing, commercially-available or proprietary library of naturally-occurring or non-natural chemical compounds; rational design of a compound based on chemical and/or structural properties of the target polynucleotide; and selection from a library of chemical compounds created combinatorially or randomly. A sample comprising a polynucleotide encoding GBAP is exposed to at least one test compound thus obtained. The sample may comprise, for example, an intact or permeabilized cell, or an *in vitro* cell-free or reconstituted biochemical system. Alterations in the expression of a polynucleotide encoding GBAP are assayed by any method commonly known in the art. Typically, the expression of a specific nucleotide is detected by hybridization with a probe having a nucleotide sequence complementary to the sequence of the polynucleotide encoding GBAP. The amount of hybridization may be quantified, thus forming the basis for a comparison of the expression of the polynucleotide both with and without exposure to one or more test compounds. Detection of a change in the expression of a polynucleotide exposed to a test compound indicates that the test compound is effective in altering the expression of

the polynucleotide. A screen for a compound effective in altering expression of a specific polynucleotide can be carried out, for example, using a Schizosaccharomyces pombe gene expression system (Atkins, D. et al. (1999) U.S. Patent No. 5,932,435; Arndt, G.M. et al. (2000) Nucleic Acids Res. 28:E15) or a human cell line such as HeLa cell (Clarke, M.L. et al. (2000) Biochem. Biophys. Res. Commun. 268:8-13). A particular embodiment of the present invention involves screening a combinatorial library of oligonucleotides (such as deoxyribonucleotides, ribonucleotides, peptide nucleic acids, and modified oligonucleotides) for antisense activity against a specific polynucleotide sequence (Bruce, T.W. et al. (1997) U.S. Patent No. 5,686,242; Bruce, T.W. et al. (2000) U.S. Patent No. 6,022,691).

10 Many methods for introducing vectors into cells or tissues are available and equally suitable for use in vivo, in vitro, and ex vivo. For ex vivo therapy, vectors may be introduced into stem cells taken from the patient and clonally propagated for autologous transplant back into that same patient. Delivery by transfection, by liposome injections, or by polycationic amino polymers may be achieved using methods which are well known in the art. (See, e.g., Goldman, C.K. et al. (1997) Nat. Biotechnol. 15:462-466.)

Any of the therapeutic methods described above may be applied to any subject in need of such therapy, including, for example, mammals such as humans, dogs, cats, cows, horses, rabbits, and monkeys.

An additional embodiment of the invention relates to the administration of a pharmaceutical composition which generally comprises an active ingredient formulated with a pharmaceutically acceptable excipient. Excipients may include, for example, sugars, starches, celluloses, gums, and proteins. Various formulations are commonly known and are thoroughly discussed in the latest edition of Remington's Pharmaceutical Sciences (Maack Publishing, Easton PA). Such pharmaceutical compositions may consist of GBAP, antibodies to GBAP, and mimetics, agonists, antagonists, or inhibitors of GBAP.

25 The pharmaceutical compositions utilized in this invention may be administered by any number of routes including, but not limited to, oral, intravenous, intramuscular, intra-arterial, intramedullary, intrathecal, intraventricular, pulmonary, transdermal, subcutaneous, intraperitoneal, intranasal, enteral, topical, sublingual, or rectal means.

30 Pharmaceutical compositions for pulmonary administration may be prepared in liquid or dry powder form. These compositions are generally aerosolized immediately prior to inhalation by the patient. In the case of small molecules (e.g. traditional low molecular weight organic drugs), aerosol delivery of fast-acting formulations is well-known in the art. In the case of macromolecules (e.g. larger peptides and proteins), recent developments in the field of pulmonary delivery via the alveolar region of the lung have enabled the practical delivery of drugs such as insulin to blood circulation (see, e.g.,

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Patton, J.S. et al., U.S. Patent No. 5,997,848). Pulmonary delivery has the advantage of administration without needle injection, and obviates the need for potentially toxic penetration enhancers.

Pharmaceutical compositions suitable for use in the invention include compositions wherein the active ingredients are contained in an effective amount to achieve the intended purpose. The  
5 determination of an effective dose is well within the capability of those skilled in the art.

Specialized forms of pharmaceutical compositions may be prepared for direct intracellular delivery of macromolecules comprising GBAP or fragments thereof. For example, liposome preparations containing a cell-impermeable macromolecule may promote cell fusion and intracellular delivery of the macromolecule. Alternatively, GBAP or a fragment thereof may be joined to a short  
10 cationic N-terminal portion from the HIV Tat-1 protein. Fusion proteins thus generated have been found to transduce into the cells of all tissues, including the brain, in a mouse model system (Schwarze, S.R. et al. (1999) Science 285:1569-1572).

For any compound, the therapeutically effective dose can be estimated initially either in cell culture assays, e.g., of neoplastic cells, or in animal models such as mice, rats, rabbits, dogs, monkeys,  
15 or pigs. An animal model may also be used to determine the appropriate concentration range and route of administration. Such information can then be used to determine useful doses and routes for administration in humans.

A therapeutically effective dose refers to that amount of active ingredient, for example GBAP or fragments thereof, antibodies of GBAP, and agonists, antagonists or inhibitors of GBAP, which  
20 ameliorates the symptoms or condition. Therapeutic efficacy and toxicity may be determined by standard pharmaceutical procedures in cell cultures or with experimental animals, such as by calculating the  $ED_{50}$  (the dose therapeutically effective in 50% of the population) or  $LD_{50}$  (the dose lethal to 50% of the population) statistics. The dose ratio of toxic to therapeutic effects is the therapeutic index, which can be expressed as the  $LD_{50}/ED_{50}$  ratio. Pharmaceutical compositions which  
25 exhibit large therapeutic indices are preferred. The data obtained from cell culture assays and animal studies are used to formulate a range of dosage for human use. The dosage contained in such compositions is preferably within a range of circulating concentrations that includes the  $ED_{50}$  with little or no toxicity. The dosage varies within this range depending upon the dosage form employed, the sensitivity of the patient, and the route of administration.

30 The exact dosage will be determined by the practitioner, in light of factors related to the subject requiring treatment. Dosage and administration are adjusted to provide sufficient levels of the active moiety or to maintain the desired effect. Factors which may be taken into account include the severity of the disease state, the general health of the subject, the age, weight, and gender of the subject, time and frequency of administration, drug combination(s), reaction sensitivities, and response to therapy.  
35 Long-acting pharmaceutical compositions may be administered every 3 to 4 days, every week, or

biweekly depending on the half-life and clearance rate of the particular formulation.

Normal dosage amounts may vary from about 0.1  $\mu\text{g}$  to 100,000  $\mu\text{g}$ , up to a total dose of about 1 gram, depending upon the route of administration. Guidance as to particular dosages and methods of delivery is provided in the literature and generally available to practitioners in the art.

- 5 Those skilled in the art will employ different formulations for nucleotides than for proteins or their inhibitors. Similarly, delivery of polynucleotides or polypeptides will be specific to particular cells, conditions, locations, etc.

## DIAGNOSTICS

- In another embodiment, antibodies which specifically bind GBAP may be used for the diagnosis  
10 of disorders characterized by expression of GBAP, or in assays to monitor patients being treated with GBAP or agonists, antagonists, or inhibitors of GBAP. Antibodies useful for diagnostic purposes may be prepared in the same manner as described above for therapeutics. Diagnostic assays for GBAP include methods which utilize the antibody and a label to detect GBAP in human body fluids or in extracts of cells or tissues. The antibodies may be used with or without modification, and may be  
15 labeled by covalent or non-covalent attachment of a reporter molecule. A wide variety of reporter molecules, several of which are described above, are known in the art and may be used.

- A variety of protocols for measuring GBAP, including ELISAs, RIAs, and FACS, are known in the art and provide a basis for diagnosing altered or abnormal levels of GBAP expression. Normal or standard values for GBAP expression are established by combining body fluids or cell extracts taken  
20 from normal mammalian subjects, for example, human subjects, with antibody to GBAP under conditions suitable for complex formation. The amount of standard complex formation may be quantitated by various methods, such as photometric means. Quantities of GBAP expressed in subject, control, and disease samples from biopsied tissues are compared with the standard values. Deviation between standard and subject values establishes the parameters for diagnosing disease.

- 25 In another embodiment of the invention, the polynucleotides encoding GBAP may be used for diagnostic purposes. The polynucleotides which may be used include oligonucleotide sequences, complementary RNA and DNA molecules, and PNAs. The polynucleotides may be used to detect and quantify gene expression in biopsied tissues in which expression of GBAP may be correlated with disease. The diagnostic assay may be used to determine absence, presence, and excess expression of  
30 GBAP, and to monitor regulation of GBAP levels during therapeutic intervention.

- In one aspect, hybridization with PCR probes which are capable of detecting polynucleotide sequences, including genomic sequences, encoding GBAP or closely related molecules may be used to identify nucleic acid sequences which encode GBAP. The specificity of the probe, whether it is made from a highly specific region, e.g., the 5' regulatory region, or from a less specific region, e.g., a  
35 conserved motif, and the stringency of the hybridization or amplification will determine whether the



probe identifies only naturally occurring sequences encoding GBAP, allelic variants, or related sequences.

Probes may also be used for the detection of related sequences, and may have at least 50% sequence identity to any of the GBAP encoding sequences. The hybridization probes of the subject invention may be DNA or RNA and may be derived from the sequence of SEQ ID NO:67-132 or from genomic sequences including promoters, enhancers, and introns of the GBAP gene.

Means for producing specific hybridization probes for DNAs encoding GBAP include the cloning of polynucleotide sequences encoding GBAP or GBAP derivatives into vectors for the production of mRNA probes. Such vectors are known in the art, are commercially available, and may be used to synthesize RNA probes in vitro by means of the addition of the appropriate RNA polymerases and the appropriate labeled nucleotides. Hybridization probes may be labeled by a variety of reporter groups, for example, by radionuclides such as  $^{32}\text{P}$  or  $^{35}\text{S}$ , or by enzymatic labels, such as alkaline phosphatase coupled to the probe via avidin/biotin coupling systems, and the like.

Polynucleotide sequences encoding GBAP may be used for the diagnosis of disorders associated with expression of GBAP. Examples of such disorders include, but are not limited to, an immune system disorder such as inflammation, actinic keratosis, acquired immunodeficiency syndrome (AIDS), Addison's disease, adult respiratory distress syndrome, allergies, ankylosing spondylitis, amyloidosis, anemia, arteriosclerosis, asthma, atherosclerosis, autoimmune hemolytic anemia, autoimmune thyroiditis, bronchitis, bursitis, cholecystitis, cirrhosis, contact dermatitis, Crohn's disease, atopic dermatitis, dermatomyositis, diabetes mellitus, emphysema, erythroblastosis fetalis, erythema nodosum, atrophic gastritis, glomerulonephritis, Goodpasture's syndrome, gout, Graves' disease, Hashimoto's thyroiditis, paroxysmal nocturnal hemoglobinuria, hepatitis, hypereosinophilia, irritable bowel syndrome, episodic lymphopenia with lymphocytotoxins, mixed connective tissue disease (MCTD), multiple sclerosis, myasthenia gravis, myocardial or pericardial inflammation, myelofibrosis, osteoarthritis, osteoporosis, pancreatitis, polycythemia vera, polymyositis, psoriasis, Reiter's syndrome, rheumatoid arthritis, scleroderma, Sjögren's syndrome, systemic anaphylaxis, systemic lupus erythematosus, systemic sclerosis, primary thrombocythemia, thrombocytopenic purpura, ulcerative colitis, uveitis, Werner syndrome, complications of cancer, hemodialysis, and extracorporeal circulation, trauma, and hematopoietic cancer including lymphoma, leukemia, and myeloma; a reproductive disorder such as a disorder of prolactin production, infertility, including tubal disease, ovulatory defects, and endometriosis, a disruption of the estrous cycle, a disruption of the menstrual cycle, polycystic ovary syndrome, ovarian hyperstimulation syndrome, an endometrial or ovarian tumor, a uterine fibroid, autoimmune disorders, an ectopic pregnancy, and teratogenesis, cancer of the breast, fibrocystic breast disease, and galactorrhea, a disruption of spermatogenesis, abnormal sperm physiology, cancer of the testis, cancer of the prostate, benign

prostatic hyperplasia, prostatitis, Peyronie's disease, impotence, carcinoma of the male breast, and gynecomastia; a nervous system disorder such as epilepsy, ischemic cerebrovascular disease, stroke, cerebral neoplasms, Alzheimer's disease, Pick's disease, Huntington's disease, dementia, Parkinson's disease and other extrapyramidal disorders, amyotrophic lateral sclerosis and other motor neuron

5 disorders, progressive neural muscular atrophy, retinitis pigmentosa, hereditary ataxias, multiple sclerosis and other demyelinating diseases, bacterial and viral meningitis, brain abscess, subdural empyema, epidural abscess, suppurative intracranial thrombophlebitis, myelitis and radiculitis, viral central nervous system disease, prion diseases including kuru, Creutzfeldt-Jakob disease, and Gerstmann-Straussler-Scheinker syndrome, fatal familial insomnia, nutritional and metabolic diseases

10 of the nervous system, neurofibromatosis, tuberous sclerosis, cerebelloretinal hemangioblastomatosis, encephalotrigeminal syndrome, mental retardation and other developmental disorders of the central nervous system, cerebral palsy, neuroskeletal disorders, autonomic nervous system disorders, cranial nerve disorders, spinal cord diseases, muscular dystrophy and other neuromuscular disorders, peripheral nervous system disorders, dermatomyositis and polymyositis, inherited, metabolic,

15 endocrine, and toxic myopathies, myasthenia gravis, periodic paralysis, mental disorders including mood, anxiety, and schizophrenic disorders, akathisia, amnesia, catatonia, diabetic neuropathy, tardive dyskinesia, dystonias, paranoid psychoses, postherpetic neuralgia, and Tourette's disorder; a cell signaling disorder including endocrine disorders such as disorders of the hypothalamus and pituitary resulting from lesions such as primary brain tumors, adenomas, infarction associated with

20 pregnancy, hypophysectomy, aneurysms, vascular malformations, thrombosis, infections, immunological disorders, and complications due to head trauma; disorders associated with hyperpituitarism including acromegaly, gigantism, and syndrome of inappropriate antidiuretic hormone (ADH) secretion (SIADH) often caused by benign adenoma; disorders associated with hypothyroidism including goiter, myxedema, acute thyroiditis associated with bacterial infection;

25 disorders associated with hyperparathyroidism including Conn disease (chronic hypercalcemia); pancreatic disorders such as Type I or Type II diabetes mellitus and associated complications; disorders associated with the adrenals such as hyperplasia, carcinoma, or adenoma of the adrenal cortex, hypertension associated with alkalosis; disorders associated with gonadal steroid hormones such as: in women, abnormal prolactin production, infertility, endometriosis, perturbations of the

30 menstrual cycle, polycystic ovarian disease, hyperprolactinemia, isolated gonadotropin deficiency, amenorrhea, galactorrhea, hermaphroditism, hirsutism and virilization, breast cancer, and, in post-menopausal women, osteoporosis; and, in men, Leydig cell deficiency, male climacteric phase, and germinal cell aplasia, hypergonadal disorders associated with Leydig cell tumors, androgen resistance associated with absence of androgen receptors, syndrome of 5  $\alpha$ -reductase, and gynecomastia; and a

35 cell proliferative disorder such as actinic keratosis, arteriosclerosis, atherosclerosis, bursitis, cirrhosis, hepatitis, mixed connective tissue disease (MCTD), myelofibrosis, paroxysmal nocturnal

hemoglobinuria, polycythemia vera, psoriasis, primary thrombocythemia, and cancers including adenocarcinoma, leukemia, lymphoma, melanoma, myeloma, sarcoma, teratocarcinoma, and, in particular, cancers of the adrenal gland, bladder, bone, bone marrow, brain, breast, cervix, gall bladder, ganglia, gastrointestinal tract, heart, kidney, liver, lung, muscle, ovary, pancreas, parathyroid, 5 penis, prostate, salivary glands, skin, spleen, testis, thymus, thyroid, and uterus. The polynucleotide sequences encoding GBAP may be used in Southern or northern analysis, dot blot, or other membrane-based technologies; in PCR technologies; in dipstick, pin, and multiformat ELISA-like assays; and in microarrays utilizing fluids or tissues from patients to detect altered GBAP expression. Such qualitative or quantitative methods are well known in the art.

10 In a particular aspect, the nucleotide sequences encoding GBAP may be useful in assays that detect the presence of associated disorders, particularly those mentioned above. The nucleotide sequences encoding GBAP may be labeled by standard methods and added to a fluid or tissue sample from a patient under conditions suitable for the formation of hybridization complexes. After a suitable incubation period, the sample is washed and the signal is quantified and compared with a standard 15 value. If the amount of signal in the patient sample is significantly altered in comparison to a control sample then the presence of altered levels of nucleotide sequences encoding GBAP in the sample indicates the presence of the associated disorder. Such assays may also be used to evaluate the efficacy of a particular therapeutic treatment regimen in animal studies, in clinical trials, or to monitor the treatment of an individual patient.

20 In order to provide a basis for the diagnosis of a disorder associated with expression of GBAP, a normal or standard profile for expression is established. This may be accomplished by combining body fluids or cell extracts taken from normal subjects, either animal or human, with a sequence, or a fragment thereof, encoding GBAP, under conditions suitable for hybridization or amplification. Standard hybridization may be quantified by comparing the values obtained from normal subjects with 25 values from an experiment in which a known amount of a substantially purified polynucleotide is used. Standard values obtained in this manner may be compared with values obtained from samples from patients who are symptomatic for a disorder. Deviation from standard values is used to establish the presence of a disorder.

Once the presence of a disorder is established and a treatment protocol is initiated, 30 hybridization assays may be repeated on a regular basis to determine if the level of expression in the patient begins to approximate that which is observed in the normal subject. The results obtained from successive assays may be used to show the efficacy of treatment over a period ranging from several days to months.

With respect to cancer, the presence of an abnormal amount of transcript (either under- or 35 overexpressed) in biopsied tissue from an individual may indicate a predisposition for the development

of the disease, or may provide a means for detecting the disease prior to the appearance of actual clinical symptoms. A more definitive diagnosis of this type may allow health professionals to employ preventative measures or aggressive treatment earlier thereby preventing the development or further progression of the cancer.

- 5 Additional diagnostic uses for oligonucleotides designed from the sequences encoding GBAP may involve the use of PCR. These oligomers may be chemically synthesized, generated enzymatically, or produced in vitro. Oligomers will preferably contain a fragment of a polynucleotide encoding GBAP, or a fragment of a polynucleotide complementary to the polynucleotide encoding GBAP, and will be employed under optimized conditions for identification of a specific gene or condition.
- 10 Oligomers may also be employed under less stringent conditions for detection or quantification of closely related DNA or RNA sequences.

In a particular aspect, oligonucleotide primers derived from the polynucleotide sequences encoding GBAP may be used to detect single nucleotide polymorphisms (SNPs). SNPs are substitutions, insertions and deletions that are a frequent cause of inherited or acquired genetic disease

15 in humans. Methods of SNP detection include, but are not limited to, single-stranded conformation polymorphism (SSCP) and fluorescent SSCP (fSSCP) methods. In SSCP, oligonucleotide primers derived from the polynucleotide sequences encoding GBAP are used to amplify DNA using the polymerase chain reaction (PCR). The DNA may be derived, for example, from diseased or normal tissue, biopsy samples, bodily fluids, and the like. SNPs in the DNA cause differences in the secondary

20 and tertiary structures of PCR products in single-stranded form, and these differences are detectable using gel electrophoresis in non-denaturing gels. In fSSCP, the oligonucleotide primers are fluorescently labeled, which allows detection of the amplimers in high-throughput equipment such as DNA sequencing machines. Additionally, sequence database analysis methods, termed *in silico* SNP (isSNP), are capable of identifying polymorphisms by comparing the sequence of individual

25 overlapping DNA fragments which assemble into a common consensus sequence. These computer-based methods filter out sequence variations due to laboratory preparation of DNA and sequencing errors using statistical models and automated analyses of DNA sequence chromatograms. In the alternative, SNPs may be detected and characterized by mass spectrometry using, for example, the high throughput MASSARRAY system (Sequenom, Inc., San Diego CA).

- 30 Methods which may also be used to quantify the expression of GBAP include radiolabeling or biotinylating nucleotides, coamplification of a control nucleic acid, and interpolating results from standard curves. (See, e.g., Melby, P.C. et al. (1993) J. Immunol. Methods 159:235-244; Duplaa, C. et al. (1993) Anal. Biochem. 212:229-236.) The speed of quantitation of multiple samples may be accelerated by running the assay in a high-throughput format where the oligomer or polynucleotide of
- 35 interest is presented in various dilutions and a spectrophotometric or colorimetric response gives rapid

quantitation.

In further embodiments, oligonucleotides or longer fragments derived from any of the polynucleotide sequences described herein may be used as elements on a microarray. The microarray can be used in transcript imaging techniques which monitor the relative expression levels of large numbers of genes simultaneously as described in Seilhamer, J.J. et al., "Comparative Gene Transcript Analysis," U.S. Patent No. 5,840,484, incorporated herein by reference. The microarray may also be used to identify genetic variants, mutations, and polymorphisms. This information may be used to determine gene function, to understand the genetic basis of a disorder, to diagnose a disorder, to monitor progression/regression of disease as a function of gene expression, and to develop and monitor the activities of therapeutic agents in the treatment of disease. In particular, this information may be used to develop a pharmacogenomic profile of a patient in order to select the most appropriate and effective treatment regimen for that patient. For example, therapeutic agents which are highly effective and display the fewest side effects may be selected for a patient based on his/her pharmacogenomic profile.

In another embodiment, antibodies specific for GBAP, or GBAP or fragments thereof may be used as elements on a microarray. The microarray may be used to monitor or measure protein-protein interactions, drug-target interactions, and gene expression profiles, as described above.

A particular embodiment relates to the use of the polynucleotides of the present invention to generate a transcript image of a tissue or cell type. A transcript image represents the global pattern of gene expression by a particular tissue or cell type. Global gene expression patterns are analyzed by quantifying the number of expressed genes and their relative abundance under given conditions and at a given time. (See Seilhamer et al., "Comparative Gene Transcript Analysis," U.S. Patent Number 5,840,484, expressly incorporated by reference herein.) Thus a transcript image may be generated by hybridizing the polynucleotides of the present invention or their complements to the totality of transcripts or reverse transcripts of a particular tissue or cell type. In one embodiment, the hybridization takes place in high-throughput format, wherein the polynucleotides of the present invention or their complements comprise a subset of a plurality of elements on a microarray. The resultant transcript image would provide a profile of gene activity.

Transcript images may be generated using transcripts isolated from tissues, cell lines, biopsies, or other biological samples. The transcript image may thus reflect gene expression in vivo, as in the case of a tissue or biopsy sample, or in vitro, as in the case of a cell line.

Transcript images which profile the expression of the polynucleotides of the present invention may also be used in conjunction with in vitro model systems and preclinical evaluation of pharmaceuticals, as well as toxicological testing of industrial and naturally-occurring environmental compounds. All compounds induce characteristic gene expression patterns, frequently termed molecular fingerprints or toxicant signatures, which are indicative of mechanisms of action and toxicity

(Nuwaysir, E.F. et al. (1999) Mol. Carcinog. 24:153-159; Steiner, S. and N.L. Anderson (2000) Toxicol. Lett. 112-113:467-471, expressly incorporated by reference herein). If a test compound has a signature similar to that of a compound with known toxicity, it is likely to share those toxic properties. These fingerprints or signatures are most useful and refined when they contain expression information from a large number of genes and gene families. Ideally, a genome-wide measurement of expression provides the highest quality signature. Even genes whose expression is not altered by any tested compounds are important as well, as the levels of expression of these genes are used to normalize the rest of the expression data. The normalization procedure is useful for comparison of expression data after treatment with different compounds. While the assignment of gene function to elements of a toxicant signature aids in interpretation of toxicity mechanisms, knowledge of gene function is not necessary for the statistical matching of signatures which leads to prediction of toxicity. (See, for example, Press Release 00-02 from the National Institute of Environmental Health Sciences, released February 29, 2000, available at <http://www.niehs.nih.gov/oc/news/toxchip.htm>.) Therefore, it is important and desirable in toxicological screening using toxicant signatures to include all expressed gene sequences.

In one embodiment, the toxicity of a test compound is assessed by treating a biological sample containing nucleic acids with the test compound. Nucleic acids that are expressed in the treated biological sample are hybridized with one or more probes specific to the polynucleotides of the present invention, so that transcript levels corresponding to the polynucleotides of the present invention may be quantified. The transcript levels in the treated biological sample are compared with levels in an untreated biological sample. Differences in the transcript levels between the two samples are indicative of a toxic response caused by the test compound in the treated sample.

Another particular embodiment relates to the use of the polypeptide sequences of the present invention to analyze the proteome of a tissue or cell type. The term proteome refers to the global pattern of protein expression in a particular tissue or cell type. Each protein component of a proteome can be subjected individually to further analysis. Proteome expression patterns, or profiles, are analyzed by quantifying the number of expressed proteins and their relative abundance under given conditions and at a given time. A profile of a cell's proteome may thus be generated by separating and analyzing the polypeptides of a particular tissue or cell type. In one embodiment, the separation is achieved using two-dimensional gel electrophoresis, in which proteins from a sample are separated by isoelectric focusing in the first dimension, and then according to molecular weight by sodium dodecyl sulfate slab gel electrophoresis in the second dimension (Steiner and Anderson, *supra*). The proteins are visualized in the gel as discrete and uniquely positioned spots, typically by staining the gel with an agent such as Coomassie Blue or silver or fluorescent stains. The optical density of each protein spot is generally proportional to the level of the protein in the sample. The optical densities of equivalently

positioned protein spots from different samples, for example, from biological samples either treated or untreated with a test compound or therapeutic agent, are compared to identify any changes in protein spot density related to the treatment. The proteins in the spots are partially sequenced using, for example, standard methods employing chemical or enzymatic cleavage followed by mass spectrometry.

- 5 The identity of the protein in a spot may be determined by comparing its partial sequence, preferably of at least 5 contiguous amino acid residues, to the polypeptide sequences of the present invention. In some cases, further sequence data may be obtained for definitive protein identification.

A proteomic profile may also be generated using antibodies specific for GBAP to quantify the levels of GBAP expression. In one embodiment, the antibodies are used as elements on a microarray, and protein expression levels are quantified by exposing the microarray to the sample and detecting the levels of protein bound to each array element (Lueking, A. et al. (1999) *Anal. Biochem.* 270:103-111; Mendoz, L.G. et al. (1999) *Biotechniques* 27:778-788). Detection may be performed by a variety of methods known in the art, for example, by reacting the proteins in the sample with a thiol- or amino-reactive fluorescent compound and detecting the amount of fluorescence bound at each array element.

- 15 Toxicant signatures at the proteome level are also useful for toxicological screening, and should be analyzed in parallel with toxicant signatures at the transcript level. There is a poor correlation between transcript and protein abundances for some proteins in some tissues (Anderson, N.L. and J. Seilhamer (1997) *Electrophoresis* 18:533-537), so proteome toxicant signatures may be useful in the analysis of compounds which do not significantly affect the transcript image, but which alter the proteomic profile. In addition, the analysis of transcripts in body fluids is difficult, due to rapid degradation of mRNA, so proteomic profiling may be more reliable and informative in such cases.

In another embodiment, the toxicity of a test compound is assessed by treating a biological sample containing proteins with the test compound. Proteins that are expressed in the treated biological sample are separated so that the amount of each protein can be quantified. The amount of each protein is compared to the amount of the corresponding protein in an untreated biological sample. A difference in the amount of protein between the two samples is indicative of a toxic response to the test compound in the treated sample. Individual proteins are identified by sequencing the amino acid residues of the individual proteins and comparing these partial sequences to the polypeptides of the present invention.

In another embodiment, the toxicity of a test compound is assessed by treating a biological sample containing proteins with the test compound. Proteins from the biological sample are incubated with antibodies specific to the polypeptides of the present invention. The amount of protein recognized by the antibodies is quantified. The amount of protein in the treated biological sample is compared with the amount in an untreated biological sample. A difference in the amount of protein between the two samples is indicative of a toxic response to the test compound in the treated sample.

- 35 Microarrays may be prepared, used, and analyzed using methods known in the art. (See, e.g.,

Brennan, T.M. et al. (1995) U.S. Patent No. 5,474,796; Schena, M. et al. (1996) Proc. Natl. Acad. Sci. USA 93:10614-10619; Baldeschweiler et al. (1995) PCT application WO95/251116; Shalon, D. et al. (1995) PCT application WO95/35505; Heller, R.A. et al. (1997) Proc. Natl. Acad. Sci. USA 94:2150-2155; and Heller, M.J. et al. (1997) U.S. Patent No. 5,605,662.) Various types of microarrays are well known and thoroughly described in DNA Microarrays: A Practical Approach, M. Schena, ed. (1999) Oxford University Press, London, hereby expressly incorporated by reference.

In another embodiment of the invention, nucleic acid sequences encoding GBAP may be used to generate hybridization probes useful in mapping the naturally occurring genomic sequence. Either coding or noncoding sequences may be used, and in some instances, noncoding sequences may be preferable over coding sequences. For example, conservation of a coding sequence among members of a multi-gene family may potentially cause undesired cross hybridization during chromosomal mapping. The sequences may be mapped to a particular chromosome, to a specific region of a chromosome, or to artificial chromosome constructions, e.g., human artificial chromosomes (HACs), yeast artificial chromosomes (YACs), bacterial artificial chromosomes (BACs), bacterial P1 constructions, or single chromosome cDNA libraries. (See, e.g., Harrington, J.J. et al. (1997) Nat. Genet. 15:345-355; Price, C.M. (1993) Blood Rev. 7:127-134; and Trask, B.J. (1991) Trends Genet. 7:149-154.) Once mapped, the nucleic acid sequences of the invention may be used to develop genetic linkage maps, for example, which correlate the inheritance of a disease state with the inheritance of a particular chromosome region or restriction fragment length polymorphism (RFLP). (See, e.g., Lander, E.S. and D. Botstein (1986) Proc. Natl. Acad. Sci. USA 83:7353-7357.)

Fluorescent in situ hybridization (FISH) may be correlated with other physical and genetic map data. (See, e.g., Heinz-Ulrich, et al. (1995) in Meyers, supra, pp. 965-968.) Examples of genetic map data can be found in various scientific journals or at the Online Mendelian Inheritance in Man (OMIM) World Wide Web site. Correlation between the location of the gene encoding GBAP on a physical map and a specific disorder, or a predisposition to a specific disorder, may help define the region of DNA associated with that disorder and thus may further positional cloning efforts.

In situ hybridization of chromosomal preparations and physical mapping techniques, such as linkage analysis using established chromosomal markers, may be used for extending genetic maps. Often the placement of a gene on the chromosome of another mammalian species, such as mouse, may reveal associated markers even if the exact chromosomal locus is not known. This information is valuable to investigators searching for disease genes using positional cloning or other gene discovery techniques. Once the gene or genes responsible for a disease or syndrome have been crudely localized by genetic linkage to a particular genomic region, e.g., ataxia-telangiectasia to 11q22-23, any sequences mapping to that area may represent associated or regulatory genes for further investigation. (See, e.g., Gatti, R.A. et al. (1988) Nature 336:577-580.) The nucleotide sequence of the instant invention may



also be used to detect differences in the chromosomal location due to translocation, inversion, etc., among normal, carrier, or affected individuals.

In another embodiment of the invention, GBAP, its catalytic or immunogenic fragments, or oligopeptides thereof can be used for screening libraries of compounds in any of a variety of drug screening techniques. The fragment employed in such screening may be free in solution, affixed to a solid support, borne on a cell surface, or located intracellularly. The formation of binding complexes between GBAP and the agent being tested may be measured.

Another technique for drug screening provides for high throughput screening of compounds having suitable binding affinity to the protein of interest. (See, e.g., Geysen, et al. (1984) PCT application WO84/03564.) In this method, large numbers of different small test compounds are synthesized on a solid substrate. The test compounds are reacted with GBAP, or fragments thereof, and washed. Bound GBAP is then detected by methods well known in the art. Purified GBAP can also be coated directly onto plates for use in the aforementioned drug screening techniques. Alternatively, non-neutralizing antibodies can be used to capture the peptide and immobilize it on a solid support.

In another embodiment, one may use competitive drug screening assays in which neutralizing antibodies capable of binding GBAP specifically compete with a test compound for binding GBAP. In this manner, antibodies can be used to detect the presence of any peptide which shares one or more antigenic determinants with GBAP.

In additional embodiments, the nucleotide sequences which encode GBAP may be used in any molecular biology techniques that have yet to be developed, provided the new techniques rely on properties of nucleotide sequences that are currently known, including, but not limited to, such properties as the triplet genetic code and specific base pair interactions.

Without further elaboration, it is believed that one skilled in the art can, using the preceding description, utilize the present invention to its fullest extent. The following preferred specific embodiments are, therefore, to be construed as merely illustrative, and not limitative of the remainder of the disclosure in any way whatsoever.

The disclosures of all patents, applications and publications, mentioned above and below, in particular U.S. Ser. No. 60/144,595, U.S. Ser. No. 60/150,460, and U.S. Ser. No. 60/159,849, are hereby expressly incorporated by reference.

## EXAMPLES

### I. Construction of cDNA Libraries

RNA was purchased from Clontech or isolated from tissues described in Table 4. Some tissues were homogenized and lysed in guanidinium isothiocyanate, while others were homogenized and lysed in phenol or in a suitable mixture of denaturants, such as TRIZOL (Life Technologies), a monophasic

solution of phenol and guanidine isothiocyanate. The resulting lysates were centrifuged over CsCl cushions or extracted with chloroform. RNA was precipitated from the lysates with either isopropanol or sodium acetate and ethanol, or by other routine methods.

Phenol extraction and precipitation of RNA were repeated as necessary to increase RNA  
5 purity. In some cases, RNA was treated with DNase. For most libraries, poly(A+) RNA was isolated using oligo d(T)-coupled paramagnetic particles (Promega), OLIGOTEX latex particles (QIAGEN, Chatsworth CA), or an OLIGOTEX mRNA purification kit (QIAGEN). Alternatively, RNA was isolated directly from tissue lysates using other RNA isolation kits, e.g., the POLY(A)PURE mRNA purification kit (Ambion, Austin TX).

10 In some cases, Stratagene was provided with RNA and constructed the corresponding cDNA libraries. Otherwise, cDNA was synthesized and cDNA libraries were constructed with the UNIZAP vector system (Stratagene) or SUPERScript plasmid system (Life Technologies), using the recommended procedures or similar methods known in the art. (See, e.g., Ausubel, 1997, supra, units 5.1-6.6.) Reverse transcription was initiated using oligo d(T) or random primers. Synthetic  
15 oligonucleotide adapters were ligated to double stranded cDNA, and the cDNA was digested with the appropriate restriction enzyme or enzymes. For most libraries, the cDNA was size-selected (300-1000 bp) using SEPHACRYL S1000, SEPHAROSE CL2B, or SEPHAROSE CL4B column chromatography (Amersham Pharmacia Biotech) or preparative agarose gel electrophoresis. cDNAs were ligated into compatible restriction enzyme sites of the polylinker of a suitable plasmid, e.g.,  
20 PBLUEScript plasmid (Stratagene), PSPORT1 plasmid (Life Technologies), pcDNA2.1 plasmid (Invitrogen, Carlsbad CA), or pINCY plasmid (Incyte Genomics, Palo Alto CA). Recombinant plasmids were transformed into competent *E. coli* cells including XL1-Blue, XL1-BlueMRF, or SOLR from Stratagene or DH5 $\alpha$ , DH10B, or ElectroMAX DH10B from Life Technologies.

## II. Isolation of cDNA Clones

25 Plasmids obtained as described in Example I were recovered from host cells by in vivo excision using the UNIZAP vector system (Stratagene) or by cell lysis. Plasmids were purified using at least one of the following: a Magic or WIZARD Minipreps DNA purification system (Promega); an AGTC Miniprep purification kit (Edge Biosystems, Gaithersburg MD); and QIAWELL 8 Plasmid, QIAWELL 8 Plus Plasmid, QIAWELL 8 Ultra Plasmid purification systems or the R.E.A.L. PREP 96 plasmid  
30 purification kit from QIAGEN. Following precipitation, plasmids were resuspended in 0.1 ml of distilled water and stored, with or without lyophilization, at 4°C.

Alternatively, plasmid DNA was amplified from host cell lysates using direct link PCR in a high-throughput format (Rao, V.B. (1994) Anal. Biochem. 216:1-14). Host cell lysis and thermal cycling steps were carried out in a single reaction mixture. Samples were processed and stored in 384-  
35 well plates, and the concentration of amplified plasmid DNA was quantified fluorometrically using

PICOGREEN dye (Molecular Probes, Eugene OR) and a FLUOROSKAN II fluorescence scanner (Labsystems Oy, Helsinki, Finland).

### III. Sequencing and Analysis

Incyte cDNA recovered in plasmids as described in Example II were sequenced as follows.

5 Sequencing reactions were processed using standard methods or high-throughput instrumentation such as the ABI CATALYST 800 (PE Biosystems) thermal cycler or the PTC-200 thermal cycler (MJ Research) in conjunction with the HYDRA microdispenser (Robbins Scientific) or the MICROLAB 2200 (Hamilton) liquid transfer system. cDNA sequencing reactions were prepared using reagents provided by Amersham Pharmacia Biotech or supplied in ABI sequencing kits such as the ABI  
10 PRISM BIGDYE Terminator cycle sequencing ready reaction kit (PE Biosystems). Electrophoretic separation of cDNA sequencing reactions and detection of labeled polynucleotides were carried out using the MEGABACE 1000 DNA sequencing system (Molecular Dynamics); the ABI PRISM 373 or 377 sequencing system (PE Biosystems) in conjunction with standard ABI protocols and base calling software; or other sequence analysis systems known in the art. Reading frames within the cDNA  
15 sequences were identified using standard methods (reviewed in Ausubel, 1997, supra, unit 7.7). Some of the cDNA sequences were selected for extension using the techniques disclosed in Example VI.

The polynucleotide sequences derived from cDNA sequencing were assembled and analyzed using a combination of software programs which utilize algorithms well known to those skilled in the art. Table 5 summarizes the tools, programs, and algorithms used and provides applicable descriptions,  
20 references, and threshold parameters. The first column of Table 5 shows the tools, programs, and algorithms used, the second column provides brief descriptions thereof, the third column presents appropriate references, all of which are incorporated by reference herein in their entirety, and the fourth column presents, where applicable, the scores, probability values, and other parameters used to evaluate the strength of a match between two sequences (the higher the score, the greater the homology between  
25 two sequences). Sequences were analyzed using MACDNASIS PRO software (Hitachi Software Engineering, South San Francisco CA) and LASERGENE software (DNASTAR). Polynucleotide and polypeptide sequence alignments were generated using the default parameters specified by the clustal algorithm as incorporated into the MEGALIGN multisequence alignment program (DNASTAR), which also calculates the percent identity between aligned sequences.

30 The polynucleotide sequences were validated by removing vector, linker, and polyA sequences and by masking ambiguous bases, using algorithms and programs based on BLAST, dynamic programing, and dinucleotide nearest neighbor analysis. The sequences were then queried against a selection of public databases such as the GenBank primate, rodent, mammalian, vertebrate, and eukaryote databases, and BLOCKS, PRINTS, DOMO, PRODOM, and PFAM to acquire annotation  
35 using programs based on BLAST, FASTA, and BLIMPS. The sequences were assembled into full

length polynucleotide sequences using programs based on Phred, Phrap, and Consed, and were screened for open reading frames using programs based on GeneMark, BLAST, and FASTA. The full length polynucleotide sequences were translated to derive the corresponding full length amino acid sequences, and these full length sequences were subsequently analyzed by querying against databases such as the  
 5 GenBank databases (described above), SwissProt, BLOCKS, PRINTS, DOMO, PRODOM, Prosite, and Hidden Markov Model (HMM)-based protein family databases such as PFAM. HMM is a probabilistic approach which analyzes consensus primary structures of gene families. (See, e.g., Eddy, S.R. (1996) Curr. Opin. Struct. Biol. 6:361-365.)

The programs described above for the assembly and analysis of full length polynucleotide and  
 10 amino acid sequences were also used to identify polynucleotide sequence fragments from SEQ ID NO:67-132. Fragments from about 20 to about 4000 nucleotides which are useful in hybridization and amplification technologies were described in The Invention section above.

#### IV. Analysis of Polynucleotide Expression

Northern analysis is a laboratory technique used to detect the presence of a transcript of a gene  
 15 and involves the hybridization of a labeled nucleotide sequence to a membrane on which RNAs from a particular cell type or tissue have been bound. (See, e.g., Sambrook, supra, ch. 7; Ausubel, 1995, supra, ch. 4 and 16.)

Analogous computer techniques applying BLAST were used to search for identical or related molecules in cDNA databases such as GenBank or LIFESEQ (Incyte Genomics). This analysis is  
 20 much faster than multiple membrane-based hybridizations. In addition, the sensitivity of the computer search can be modified to determine whether any particular match is categorized as exact or similar. The basis of the search is the product score, which is defined as:

$$\frac{\text{BLAST Score} \times \text{Percent Identity}}{5 \times \text{minimum \{length(Seq. 1), length(Seq. 2)\}}}$$

25

The product score takes into account both the degree of similarity between two sequences and the length of the sequence match. The product score is a normalized value between 0 and 100, and is calculated as follows: the BLAST score is multiplied by the percent nucleotide identity and the product is divided by (5 times the length of the shorter of the two sequences). The BLAST score is calculated by  
 30 assigning a score of +5 for every base that matches in a high-scoring segment pair (HSP), and -4 for every mismatch. Two sequences may share more than one HSP (separated by gaps). If there is more than one HSP, then the pair with the highest BLAST score is used to calculate the product score. The product score represents a balance between fractional overlap and quality in a BLAST alignment. For example, a product score of 100 is produced only for 100% identity over the entire length of the shorter  
 35 of the two sequences being compared. A product score of 70 is produced either by 100% identity and

70% overlap at one end, or by 88% identity and 100% overlap at the other. A product score of 50 is produced either by 100% identity and 50% overlap at one end, or 79% identity and 100% overlap.

The results of northern analyses are reported as a percentage distribution of libraries in which the transcript encoding GBAP occurred. Analysis involved the categorization of cDNA libraries by organ/tissue and disease. The organ/tissue categories included cardiovascular, dermatologic, developmental, endocrine, gastrointestinal, hematopoietic/immune, musculoskeletal, nervous, reproductive, and urologic. The disease/condition categories included cancer, inflammation, trauma, cell proliferation, neurological, and pooled. For each category, the number of libraries expressing the sequence of interest was counted and divided by the total number of libraries across all categories. Percentage values of tissue-specific and disease- or condition-specific expression are reported in Table 3.

#### V. Chromosomal Mapping of GBAP Encoding Polynucleotides

The cDNA sequences which were used to assemble SEQ ID NO:67-132 were compared with sequences from the Incyte LIFESEQ database and public domain databases using BLAST and other implementations of the Smith-Waterman algorithm. Sequences from these databases that matched SEQ ID NO:67-132 were assembled into clusters of contiguous and overlapping sequences using assembly algorithms such as Phrap (Table 5). Radiation hybrid and genetic mapping data available from public resources such as the Stanford Human Genome Center (SHGC), Whitehead Institute for Genome Research (WIGR), and Généthon were used to determine if any of the clustered sequences had been previously mapped. Inclusion of a mapped sequence in a cluster resulted in the assignment of all sequences of that cluster, including its particular SEQ ID NO:, to that map location.

The genetic map locations of SEQ ID NO:70, 74, 75, 77, 80, 86, 87, 90, 92, 93, 94, 97, 101, 106, 109, 111, 112, 113, 115, 117, 118, 121, and 128 are described in The Invention as ranges, or intervals, of human chromosomes. More than one map location is reported for SEQ ID NO:94, 101, 109, 111, and 115, indicating that previously mapped sequences having similarity, but not complete identity, to SEQ ID NO:94, 101, 109, 111, and 115 were assembled into their respective clusters. The map position of an interval, in centiMorgans, is measured relative to the terminus of the chromosome's p-arm. (The centiMorgan (cM) is a unit of measurement based on recombination frequencies between chromosomal markers. On average, 1 cM is roughly equivalent to 1 megabase (Mb) of DNA in humans, although this can vary widely due to hot and cold spots of recombination.) The cM distances are based on genetic markers mapped by Généthon which provide boundaries for radiation hybrid markers whose sequences were included in each of the clusters.

#### VI. Extension of GBAP Encoding Polynucleotides

The full length nucleic acid sequences of SEQ ID NO:67-132 were produced by extension of an appropriate fragment of the full length molecule using oligonucleotide primers designed from this

fragment. One primer was synthesized to initiate 5' extension of the known fragment, and the other primer, to initiate 3' extension of the known fragment. The initial primers were designed using OLIGO 4.06 software (National Biosciences), or another appropriate program, to be about 22 to 30 nucleotides in length, to have a GC content of about 50% or more, and to anneal to the target sequence at 5 temperatures of about 68°C to about 72°C. Any stretch of nucleotides which would result in hairpin structures and primer-primer dimerizations was avoided.

Selected human cDNA libraries were used to extend the sequence. If more than one extension was necessary or desired, additional or nested sets of primers were designed.

High fidelity amplification was obtained by PCR using methods well known in the art. PCR 10 was performed in 96-well plates using the PTC-200 thermal cycler (MJ Research, Inc.). The reaction mix contained DNA template, 200 nmol of each primer, reaction buffer containing  $Mg^{2+}$ ,  $(NH_4)_2SO_4$ , and  $\beta$ -mercaptoethanol, Taq DNA polymerase (Amersham Pharmacia Biotech), ELONGASE enzyme (Life Technologies), and Pfu DNA polymerase (Stratagene), with the following parameters for primer pair PCI A and PCI B: Step 1: 94°C, 3 min; Step 2: 94°C, 15 sec; Step 3: 60°C, 1 min; Step 4: 68°C, 15 2 min; Step 5: Steps 2, 3, and 4 repeated 20 times; Step 6: 68°C, 5 min; Step 7: storage at 4°C. In the alternative, the parameters for primer pair T7 and SK+ were as follows: Step 1: 94°C, 3 min; Step 2: 94°C, 15 sec; Step 3: 57°C, 1 min; Step 4: 68°C, 2 min; Step 5: Steps 2, 3, and 4 repeated 20 times; Step 6: 68°C, 5 min; Step 7: storage at 4°C.

The concentration of DNA in each well was determined by dispensing 100  $\mu$ l PICOGREEN 20 quantitation reagent (0.25% (v/v) PICOGREEN; Molecular Probes, Eugene OR) dissolved in 1X TE and 0.5  $\mu$ l of undiluted PCR product into each well of an opaque fluorimeter plate (Corning Costar, Acton MA), allowing the DNA to bind to the reagent. The plate was scanned in a Fluoroskan II (Labsystems Oy, Helsinki, Finland) to measure the fluorescence of the sample and to quantify the concentration of DNA. A 5  $\mu$ l to 10  $\mu$ l aliquot of the reaction mixture was analyzed by electrophoresis 25 on a 1 % agarose mini-gel to determine which reactions were successful in extending the sequence.

The extended nucleotides were desalted and concentrated, transferred to 384-well plates, digested with CviJI cholera virus endonuclease (Molecular Biology Research, Madison WI), and sonicated or sheared prior to religation into pUC 18 vector (Amersham Pharmacia Biotech). For shotgun sequencing, the digested nucleotides were separated on low concentration (0.6 to 0.8%) agarose 30 gels, fragments were excised, and agar digested with Agar ACE (Promega). Extended clones were religated using T4 ligase (New England Biolabs, Beverly MA) into pUC 18 vector (Amersham Pharmacia Biotech), treated with Pfu DNA polymerase (Stratagene) to fill-in restriction site overhangs, and transfected into competent *E. coli* cells. Transformed cells were selected on antibiotic-containing media, and individual colonies were picked and cultured overnight at 37°C in 384-well plates in LB/2x 35 carb liquid media.

The cells were lysed, and DNA was amplified by PCR using Taq DNA polymerase (Amersham Pharmacia Biotech) and Pfu DNA polymerase (Stratagene) with the following parameters: Step 1: 94°C, 3 min; Step 2: 94°C, 15 sec; Step 3: 60°C, 1 min; Step 4: 72°C, 2 min; Step 5: steps 2, 3, and 4 repeated 29 times; Step 6: 72°C, 5 min; Step 7: storage at 4°C. DNA was quantified by PICOGREEN reagent (Molecular Probes) as described above. Samples with low DNA recoveries were reamplified using the same conditions as described above. Samples were diluted with 20% dimethylsulfoxide (1:2, v/v), and sequenced using DYENAMIC energy transfer sequencing primers and the DYENAMIC DIRECT kit (Amersham Pharmacia Biotech) or the ABI PRISM BIGDYE Terminator cycle sequencing ready reaction kit (PE Biosystems).

10 In like manner, the polynucleotide sequences of SEQ ID NO:67-132 are used to obtain 5' regulatory sequences using the procedure above, along with oligonucleotides designed for such extension, and an appropriate genomic library.

#### VII. Labeling and Use of Individual Hybridization Probes

Hybridization probes derived from SEQ ID NO:67-132 are employed to screen cDNAs, genomic DNAs, or mRNAs. Although the labeling of oligonucleotides, consisting of about 20 base pairs, is specifically described, essentially the same procedure is used with larger nucleotide fragments. Oligonucleotides are designed using state-of-the-art software such as OLIGO 4.06 software (National Biosciences) and labeled by combining 50 pmol of each oligomer, 250  $\mu$ Ci of [ $\gamma$ -<sup>32</sup>P] adenosine triphosphate (Amersham Pharmacia Biotech), and T4 polynucleotide kinase (DuPont NEN, Boston MA). The labeled oligonucleotides are substantially purified using a SEPHADEX G-25 superfine size exclusion dextran bead column (Amersham Pharmacia Biotech). An aliquot containing 10<sup>7</sup> counts per minute of the labeled probe is used in a typical membrane-based hybridization analysis of human genomic DNA digested with one of the following endonucleases: Ase I, Bgl II, Eco RI, Pst I, Xba I, or Pvu II (DuPont NEN).

25 The DNA from each digest is fractionated on a 0.7% agarose gel and transferred to nylon membranes (Nytran Plus, Schleicher & Schuell, Durham NH). Hybridization is carried out for 16 hours at 40°C. To remove nonspecific signals, blots are sequentially washed at room temperature under conditions of up to, for example, 0.1 x saline sodium citrate and 0.5% sodium dodecyl sulfate. Hybridization patterns are visualized using autoradiography or an alternative imaging means and compared.

#### VIII. Microarrays

The linkage or synthesis of array elements upon a microarray can be achieved utilizing photolithography, piezoelectric printing (ink-jet printing, See, e.g., Baldeschweiler, *supra*), mechanical microspotting technologies, and derivatives thereof. The substrate in each of the aforementioned technologies should be uniform and solid with a non-porous surface (Skena (1999), *supra*). Suggested

substrates include silicon, silica, glass slides, glass chips, and silicon wafers. Alternatively, a procedure analogous to a dot or slot blot may also be used to arrange and link elements to the surface of a substrate using thermal, UV, chemical, or mechanical bonding procedures. A typical array may be produced using available methods and machines well known to those of ordinary skill in the art and may contain any appropriate number of elements. (See, e.g., Schena, M. et al. (1995) *Science* 270:467-470; Shalon, D. et al. (1996) *Genome Res.* 6:639-645; Marshall, A. and J. Hodgson (1998) *Nat. Biotechnol.* 16:27-31.)

Full length cDNAs, Expressed Sequence Tags (ESTs), or fragments or oligomers thereof may comprise the elements of the microarray. Fragments or oligomers suitable for hybridization can be selected using software well known in the art such as LASERGENE software (DNASTAR). The array elements are hybridized with polynucleotides in a biological sample. The polynucleotides in the biological sample are conjugated to a fluorescent label or other molecular tag for ease of detection. After hybridization, nonhybridized nucleotides from the biological sample are removed, and a fluorescence scanner is used to detect hybridization at each array element. Alternatively, laser desorption and mass spectrometry may be used for detection of hybridization. The degree of complementarity and the relative abundance of each polynucleotide which hybridizes to an element on the microarray may be assessed. In one embodiment, microarray preparation and usage is described in detail below.

#### Tissue or Cell Sample Preparation

Total RNA is isolated from tissue samples using the guanidinium thiocyanate method and poly(A)<sup>+</sup> RNA is purified using the oligo-(dT) cellulose method. Each poly(A)<sup>+</sup> RNA sample is reverse transcribed using MMLV reverse-transcriptase, 0.05 pg/ $\mu$ l oligo-(dT) primer (21mer), 1X first strand buffer, 0.03 units/ $\mu$ l RNase inhibitor, 500  $\mu$ M dATP, 500  $\mu$ M dGTP, 500  $\mu$ M dTTP, 40  $\mu$ M dCTP, 40  $\mu$ M dCTP-Cy3 (BDS) or dCTP-Cy5 (Amersham Pharmacia Biotech). The reverse transcription reaction is performed in a 25 ml volume containing 200 ng poly(A)<sup>+</sup> RNA with GEMBRIGHT kits (Incyte). Specific control poly(A)<sup>+</sup> RNAs are synthesized by in vitro transcription from non-coding yeast genomic DNA. After incubation at 37°C for 2 hr, each reaction sample (one with Cy3 and another with Cy5 labeling) is treated with 2.5 ml of 0.5M sodium hydroxide and incubated for 20 minutes at 85°C to stop the reaction and degrade the RNA. Samples are purified using two successive CHROMA SPIN 30 gel filtration spin columns (CLONTECH Laboratories, Inc. (CLONTECH), Palo Alto CA) and after combining, both reaction samples are ethanol precipitated using 1 ml of glycogen (1 mg/ml), 60 ml sodium acetate, and 300 ml of 100% ethanol. The sample is then dried to completion using a SpeedVAC (Savant Instruments Inc., Holbrook NY) and resuspended in 14  $\mu$ l 5X SSC/0.2% SDS.

#### Microarray Preparation



Sequences of the present invention are used to generate array elements. Each array element is amplified from bacterial cells containing vectors with cloned cDNA inserts. PCR amplification uses primers complementary to the vector sequences flanking the cDNA insert. Array elements are amplified in thirty cycles of PCR from an initial quantity of 1-2 ng to a final quantity greater than 5  $\mu$ g. Amplified array elements are then purified using SEPHACRYL-400 (Amersham Pharmacia Biotech).

Purified array elements are immobilized on polymer-coated glass slides. Glass microscope slides (Corning) are cleaned by ultrasound in 0.1% SDS and acetone, with extensive distilled water washes between and after treatments. Glass slides are etched in 4% hydrofluoric acid (VWR Scientific Products Corporation (VWR), West Chester PA), washed extensively in distilled water, and coated with 0.05% aminopropyl silane (Sigma) in 95% ethanol. Coated slides are cured in a 110°C oven.

Array elements are applied to the coated glass substrate using a procedure described in US Patent No. 5,807,522, incorporated herein by reference. 1  $\mu$ l of the array element DNA, at an average concentration of 100 ng/ $\mu$ l, is loaded into the open capillary printing element by a high-speed robotic apparatus. The apparatus then deposits about 5 nl of array element sample per slide.

Microarrays are UV-crosslinked using a STRATALINKER UV-crosslinker (Stratagene). Microarrays are washed at room temperature once in 0.2% SDS and three times in distilled water. Non-specific binding sites are blocked by incubation of microarrays in 0.2% casein in phosphate buffered saline (PBS) (Tropix, Inc., Bedford MA) for 30 minutes at 60 °C followed by washes in 0.2% SDS and distilled water as before.

#### Hybridization

Hybridization reactions contain 9  $\mu$ l of sample mixture consisting of 0.2  $\mu$ g each of Cy3 and Cy5 labeled cDNA synthesis products in 5X SSC, 0.2% SDS hybridization buffer. The sample mixture is heated to 65 °C for 5 minutes and is aliquoted onto the microarray surface and covered with an 1.8 cm<sup>2</sup> coverslip. The arrays are transferred to a waterproof chamber having a cavity just slightly larger than a microscope slide. The chamber is kept at 100% humidity internally by the addition of 140  $\mu$ l of 5X SSC in a corner of the chamber. The chamber containing the arrays is incubated for about 6.5 hours at 60 °C. The arrays are washed for 10 min at 45 °C in a first wash buffer (1X SSC, 0.1% SDS), three times for 10 minutes each at 45 °C in a second wash buffer (0.1X SSC), and dried.

#### Detection

Reporter-labeled hybridization complexes are detected with a microscope equipped with an Innova 70 mixed gas 10 W laser (Coherent, Inc., Santa Clara CA) capable of generating spectral lines at 488 nm for excitation of Cy3 and at 632 nm for excitation of Cy5. The excitation laser light is focused on the array using a 20X microscope objective (Nikon, Inc., Melville NY). The slide

containing the array is placed on a computer-controlled X-Y stage on the microscope and raster-scanned past the objective. The 1.8 cm x 1.8 cm array used in the present example is scanned with a resolution of 20 micrometers.

In two separate scans, a mixed gas multiline laser excites the two fluorophores sequentially. 5 Emitted light is split, based on wavelength, into two photomultiplier tube detectors (PMT R1477, Hamamatsu Photonics Systems, Bridgewater NJ) corresponding to the two fluorophores. Appropriate filters positioned between the array and the photomultiplier tubes are used to filter the signals. The emission maxima of the fluorophores used are 565 nm for Cy3 and 650 nm for Cy5. Each array is typically scanned twice, one scan per fluorophore using the appropriate filters at the laser source, 10 although the apparatus is capable of recording the spectra from both fluorophores simultaneously.

The sensitivity of the scans is typically calibrated using the signal intensity generated by a cDNA control species added to the sample mixture at a known concentration. A specific location on the array contains a complementary DNA sequence, allowing the intensity of the signal at that location to be correlated with a weight ratio of hybridizing species of 1:100,000. When two samples 15 from different sources (e.g., representing test and control cells), each labeled with a different fluorophore, are hybridized to a single array for the purpose of identifying genes that are differentially expressed, the calibration is done by labeling samples of the calibrating cDNA with the two fluorophores and adding identical amounts of each to the hybridization mixture.

The output of the photomultiplier tube is digitized using a 12-bit RTI-835H analog-to-digital 20 (A/D) conversion board (Analog Devices, Inc., Norwood MA) installed in an IBM-compatible PC computer. The digitized data are displayed as an image where the signal intensity is mapped using a linear 20-color transformation to a pseudocolor scale ranging from blue (low signal) to red (high signal). The data is also analyzed quantitatively. Where two different fluorophores are excited and measured simultaneously, the data are first corrected for optical crosstalk (due to overlapping 25 emission spectra) between the fluorophores using each fluorophore's emission spectrum.

A grid is superimposed over the fluorescence signal image such that the signal from each spot is centered in each element of the grid. The fluorescence signal within each element is then integrated to obtain a numerical value corresponding to the average intensity of the signal. The software used for signal analysis is the GEMTOOLS gene expression analysis program (Incyte).

#### 30 IX. Complementary Polynucleotides

Sequences complementary to the GBAP-encoding sequences, or any parts thereof, are used to detect, decrease, or inhibit expression of naturally occurring GBAP. Although use of oligonucleotides comprising from about 15 to 30 base pairs is described, essentially the same procedure is used with smaller or with larger sequence fragments. Appropriate oligonucleotides are designed using OLIGO 35 4.06 software (National Biosciences) and the coding sequence of GBAP. To inhibit transcription, a

complementary oligonucleotide is designed from the most unique 5' sequence and used to prevent promoter binding to the coding sequence. To inhibit translation, a complementary oligonucleotide is designed to prevent ribosomal binding to the GBAP-encoding transcript.

#### X. Expression of GBAP

5 Expression and purification of GBAP is achieved using bacterial or virus-based expression systems. For expression of GBAP in bacteria, cDNA is subcloned into an appropriate vector containing an antibiotic resistance gene and an inducible promoter that directs high levels of cDNA transcription. Examples of such promoters include, but are not limited to, the *trp-lac (tac)* hybrid promoter and the T5 or T7 bacteriophage promoter in conjunction with the *lac* operator regulatory  
10 element. Recombinant vectors are transformed into suitable bacterial hosts, e.g., BL21(DE3). Antibiotic resistant bacteria express GBAP upon induction with isopropyl beta-D-thiogalactopyranoside (IPTG). Expression of GBAP in eukaryotic cells is achieved by infecting insect or mammalian cell lines with recombinant Autographica californica nuclear polyhedrosis virus (AcMNPV), commonly known as baculovirus. The nonessential polyhedrin gene of baculovirus is  
15 replaced with cDNA encoding GBAP by either homologous recombination or bacterial-mediated transposition involving transfer plasmid intermediates. Viral infectivity is maintained and the strong polyhedrin promoter drives high levels of cDNA transcription. Recombinant baculovirus is used to infect Spodoptera frugiperda (Sf9) insect cells in most cases, or human hepatocytes, in some cases. Infection of the latter requires additional genetic modifications to baculovirus. (See Engelhard, E.K. et  
20 al. (1994) Proc. Natl. Acad. Sci. USA 91:3224-3227; Sandig, V. et al. (1996) Hum. Gene Ther. 7:1937-1945.)

In most expression systems, GBAP is synthesized as a fusion protein with, e.g., glutathione S-transferase (GST) or a peptide epitope tag, such as FLAG or 6-His, permitting rapid, single-step, affinity-based purification of recombinant fusion protein from crude cell lysates. GST, a 26-kilodalton  
25 enzyme from Schistosoma japonicum, enables the purification of fusion proteins on immobilized glutathione under conditions that maintain protein activity and antigenicity (Amersham Pharmacia Biotech). Following purification, the GST moiety can be proteolytically cleaved from GBAP at specifically engineered sites. FLAG, an 8-amino acid peptide, enables immunoaffinity purification using commercially available monoclonal and polyclonal anti-FLAG antibodies (Eastman Kodak). 6-  
30 His, a stretch of six consecutive histidine residues, enables purification on metal-chelate resins (QIAGEN). Methods for protein expression and purification are discussed in Ausubel (1995, supra, ch. 10 and 16). Purified GBAP obtained by these methods can be used directly in the assays shown in Examples XI and XV.

#### XI. Demonstration of GBAP Activity

35 GTP-binding activity of GBAP is determined in an assay that measures the binding of GBAP

to  $\alpha$ - $^{32}$ P-labeled GTP. Purified GBAP is first blotted onto filters and rinsed in a suitable buffer. The filters are then incubated in buffer containing radiolabeled  $\alpha$ - $^{32}$ P-GTP. The filters are washed in buffer to remove unbound GTP and counted in a radioisotope counter. Non-specific binding is determined in an assay that contains a 100-fold excess of unlabeled GTP. The amount of specific binding is

5 proportional to the activity of GBAP.

GTPase activity of GBAP is determined in an assay that measures the conversion of  $\alpha$ - $^{32}$ P-GTP to  $\alpha$ - $^{32}$ P-GDP. GBAP is incubated with  $\alpha$ - $^{32}$ P-GTP in buffer for an appropriate period of time, and the reaction is terminated by heating or acid precipitation followed by centrifugation. An aliquot of the supernatant is subjected to polyacrylamide gel electrophoresis (PAGE) to separate GDP and GTP  
10 together with unlabeled standards. The GDP spot is cut out and counted in a radioisotope counter. The amount of radioactivity recovered in GDP is proportional to GTPase activity of GBAP.

## **XII. Functional Assays**

GBAP function is assessed by expressing the sequences encoding GBAP at physiologically elevated levels in mammalian cell culture systems. cDNA is subcloned into a mammalian expression  
15 vector containing a strong promoter that drives high levels of cDNA expression. Vectors of choice include pCMV SPORT plasmid (Life Technologies) and pCR3.1 plasmid (Invitrogen), both of which contain the cytomegalovirus promoter. 5-10  $\mu$ g of recombinant vector are transiently transfected into a human cell line, for example, an endothelial or hematopoietic cell line, using either liposome formulations or electroporation. 1-2  $\mu$ g of an additional plasmid containing sequences encoding a  
20 marker protein are co-transfected. Expression of a marker protein provides a means to distinguish transfected cells from nontransfected cells and is a reliable predictor of cDNA expression from the recombinant vector. Marker proteins of choice include, e.g., Green Fluorescent Protein (GFP; Clontech), CD64, or a CD64-GFP fusion protein. Flow cytometry (FCM), an automated, laser optics-based technique, is used to identify transfected cells expressing GFP or CD64-GFP and to evaluate the  
25 apoptotic state of the cells and other cellular properties. FCM detects and quantifies the uptake of fluorescent molecules that diagnose events preceding or coincident with cell death. These events include changes in nuclear DNA content as measured by staining of DNA with propidium iodide; changes in cell size and granularity as measured by forward light scatter and 90 degree side light scatter; down-regulation of DNA synthesis as measured by decrease in bromodeoxyuridine uptake; alterations in  
30 expression of cell surface and intracellular proteins as measured by reactivity with specific antibodies; and alterations in plasma membrane composition as measured by the binding of fluorescein-conjugated Annexin V protein to the cell surface. Methods in flow cytometry are discussed in Ormerod, M.G. (1994) Flow Cytometry, Oxford, New York NY.

The influence of GBAP on gene expression can be assessed using highly purified populations of  
35 cells transfected with sequences encoding GBAP and either CD64 or CD64-GFP. CD64 and CD64-

GFP are expressed on the surface of transfected cells and bind to conserved regions of human immunoglobulin G (IgG). Transfected cells are efficiently separated from nontransfected cells using magnetic beads coated with either human IgG or antibody against CD64 (DYNAL, Lake Success NY). mRNA can be purified from the cells using methods well known by those of skill in the art. Expression of mRNA encoding GBAP and other genes of interest can be analyzed by northern analysis or microarray techniques.

### **XIII. Production of GBAP Specific Antibodies**

GBAP substantially purified using polyacrylamide gel electrophoresis (PAGE; see, e.g., Harrington, M.G. (1990) *Methods Enzymol.* 182:488-495), or other purification techniques, is used to immunize rabbits and to produce antibodies using standard protocols.

Alternatively, the GBAP amino acid sequence is analyzed using LASERGENE software (DNASTAR) to determine regions of high immunogenicity, and a corresponding oligopeptide is synthesized and used to raise antibodies by means known to those of skill in the art. Methods for selection of appropriate epitopes, such as those near the C-terminus or in hydrophilic regions are well described in the art. (See, e.g., Ausubel, 1995, *supra*, ch. 11.)

Typically, oligopeptides of about 15 residues in length are synthesized using an ABI 431A peptide synthesizer (PE Biosystems) using Fmoc chemistry and coupled to KLH (Sigma-Aldrich, St. Louis MO) by reaction with N-maleimidobenzoyl-N-hydroxysuccinimide ester (MBS) to increase immunogenicity. (See, e.g., Ausubel, 1995, *supra*.) Rabbits are immunized with the oligopeptide-KLH complex in complete Freund's adjuvant. Resulting antisera are tested for antipeptide and anti-GBAP activity by, for example, binding the peptide or GBAP to a substrate, blocking with 1% BSA, reacting with rabbit antisera, washing, and reacting with radio-iodinated goat anti-rabbit IgG.

### **XIV. Purification of Naturally Occurring GBAP Using Specific Antibodies**

Naturally occurring or recombinant GBAP is substantially purified by immunoaffinity chromatography using antibodies specific for GBAP. An immunoaffinity column is constructed by covalently coupling anti-GBAP antibody to an activated chromatographic resin, such as CNBr-activated SEPHAROSE (Amersham Pharmacia Biotech). After the coupling, the resin is blocked and washed according to the manufacturer's instructions.

Media containing GBAP are passed over the immunoaffinity column, and the column is washed under conditions that allow the preferential absorbance of GBAP (e.g., high ionic strength buffers in the presence of detergent). The column is eluted under conditions that disrupt antibody/GBAP binding (e.g., a buffer of pH 2 to pH 3, or a high concentration of a chaotrope, such as urea or thiocyanate ion), and GBAP is collected.

### **XV. Identification of Molecules Which Interact with GBAP**

GBAP, or biologically active fragments thereof, are labeled with <sup>125</sup>I Bolton-Hunter reagent.

(See, e.g., Bolton A.E. and W.M. Hunter (1973) *Biochem. J.* 133:529-539.) Candidate molecules previously arrayed in the wells of a multi-well plate are incubated with the labeled GBAP, washed, and any wells with labeled GBAP complex are assayed. Data obtained using different concentrations of GBAP are used to calculate values for the number, affinity, and association of GBAP with the

5 candidate molecules.

Alternatively, molecules interacting with GBAP are analyzed using the yeast two-hybrid system as described in Fields, S. and O. Song (1989, *Nature* 340:245-246), or using commercially available kits based on the two-hybrid system, such as the MATCHMAKER system (Clontech).

GBAP may also be used in the PATHCALLING process (CuraGen Corp., New Haven CT)

10 which employs the yeast two-hybrid system in a high-throughput manner to determine all interactions between the proteins encoded by two large libraries of genes (Nandabalan, K. et al. (2000) U.S. Patent No. 6,057,101).

Various modifications and variations of the described methods and systems of the invention will

15 be apparent to those skilled in the art without departing from the scope and spirit of the invention.

Although the invention has been described in connection with certain embodiments, it should be understood that the invention as claimed should not be unduly limited to such specific embodiments. Indeed, various modifications of the described modes for carrying out the invention which are obvious to those skilled in molecular biology or related fields are intended to be within the scope of the following

20 claims.

Table 1

Protein SEQ ID No.:	Nucleotide SEQ ID NO:	Clone ID	Library	Fragments
1	67	1405545	LATRTUT02	1405545F6 (LATRTUT02), 1405545H1 (LATRTUT02), 2926327F7 (TLYMNOT04), 2926327T6 (TLYMNOT04)
2	68	1451265	PENITUT01	700515X14 (SYNORAT03), 758541H1 (BRAITUT02), 1348685F6 (PROSNOT11), 1451265H1 (PENITUT01), 1872777F6 (LEUKNOT02)
3	69	1556311	BLADTUT04	1556311H1 (BLADTUT04), 3221281T6 (COLNNOT03), 3350311F6 (BRAITUT24), SBFA02256F1, SBFA01440F1, SBFA01098F1, SBFA04741F1
4	70	1901373	BLADTUT06	758057H1 (BRAITUT02), 1255886H1 (MENITUT03), 1887731X12C1 (BLADTUT07), 1901373H1 (BLADTUT06), 2866863H1 (KIDNNOT20), 3090943H1 (BRSTNOT19), 3215237H1 (TESTNOT07), 3719233H1 (PENCNOT10), 4319601H1 (BRADDIT02)
5	71	2367767	ADRENOT07	1331124F1 (PANCNOT07), 2367767H1 (ADRENOT07), 2367779F6 (ADRENOT07), 2782232F6 (BRSTNOT13), 3079286H2 (BRAIUNT01), 3584043T6 (293TF4T01), 4994696H1 (LIVRTUT11)
6	72	3090433	BRSTNOT19	312565H1 (LUNGNOT02), 841829R6 (PROSTUT05), 1340809H1 (COLNTUT03), 1842057H1 (COLNNOT07), 2693513F6 (LUNGNOT23), 3090433H1 (BRSTNOT19), 4895874H1 (LIVRTUT12)
7	73	3800591	SPLNNOT12	554715F1 (SCORNOT01), 882035X23 (THYRNOT02), 3042234F7 (BRSTNOT16), 3630695H1 (COLNNOT38), 3800591H1 (SPLNNOT12), 4975447H1 (HELATXT03)
8	74	5308471	MONOTXT02	790680R1 (PROSTUT03), 870507R1 (LUNGAST01), 948177R1 (PANCNOT05), 1682469T7 (PROSNOT15), 2897215H1 (KIDNTUT14), 5308471H1 (MONOTXT02)
9	75	5324322	FIBPFEN06	1001977R1 (BRSTNOT03), 1312045F1 (COLNFET02), 1334040F2 (COLNNOT13), 1488082F6 (UCMCL5T01), 1570077F1 (UTRSNOT05), 1929845H1 (COLNTUT03), 2306061H1 (NGANNOT01), 3127730F7 (LUNGUTUT12), 3494367H1 (ADRETUT07), 3578924H1 (293TF3T01), 4619513H1 (ENDVNOT01), 4932823H1 (BRSTTUT20), 5324322H1 (FIBPFEN06)
10	76	067184	HUVESTB01	067184H1 (HUVESTB01), 067184R1 (HUVESTB01), 067184X12 (HUVESTB01), 067184X23C1 (HUVESTB01), 067184X29C1 (HUVESTB01), 968551H1 (BRSTNOT05), 2611874T6 (LUNGUTUT10)
11	77	722896	SYNOOAT01	722896H1 (SYNOOAT01), 722896X19C1 (SYNOOAT01), 1433775T1 (BEPINON01), 1477633T6 (CORPNOT02), 2676923F6 (KIDNNOT19), 3230945H1 (COTRNOT01), 3389989H1 (LUNGUTUT17)
12	78	1571739	UTRSNOT05	1571739H1 (UTRSNOT05), 1571739X12R1 (UTRSNOT05), 2799982H1 (PENCNOT01), 4059114F6 (BRAIINOT21)

Table 1 (cont.)

Protein SEQ ID NO:	Nucleotide SEQ ID NO:	Clone ID	Library	Fragments
13	79	1739479	HIPONON01	511157H1 (MPHGNOT03), 511157T6 (MPHGNOT03), 1739479H1 (HIPONON01), 2092446T6 (PANCNOT04), 3880948F6 (SPLNNOT11)
14	80	1999147	BRSTTUT03	1339243T6 (COLNTUT03), 1999147H1 (BRSTTUT03), 2094940X11F1 (BRAITUT02), 2670959T6 (ESOGTUT02), 3297709H1 (TLYJINT01), 3396927H1 (UTRSNOT16), SCBA00828V1, SCBA00615V1, SCBA04422V1, SCBA04646V1, SCBA01715V1, 5544151H1 (TESTNOC01)
15	81	2182085	SININOT01	767764R6 (LUNGNOT04), 1655010F6 (PROSTUT08), 1701703T6 (BLADTUT05), 1871360F6 (SKINBIT01), 2081835F6 (UTRSNOT08), 2411644H1 (BSTMNON02)
16	82	2216640	SINTFET03	489759H1 (HNT2AGT01), 2057454T6 (BEPINOT01), 2097739H1 (BRAITUT02), 2216640H1 (SINTFET03), 2325135H1 (OVARNOT02), 2361273R6 (LUNGFET05), 2667958H1 (ESOGTUT02), 3462348H1 (293TF2T01), 3478754H1 (OVARNOT11), 4163069F6 (BRSTNOT32)
17	83	2417361	HNT3AZT01	1394742F1 (THYRNOT03), 2417361F6 (HNT3AZT01), 2417361H1 (HNT3AZT01)
18	84	2454384	ENDANOT01	2454384H1 (ENDANOT01), 2454384T6 (ENDANOT01), 2589653T6 (LUNGNOT22), 2643485F6 (LUNGUTUT08), 2723048H1 (LUNGUTUT10), 3130367H1 (LUNGUTUT12)
19	85	2610262	LUNGUTUT08	1226946R6 (COLNNOT01), 1226946T6 (COLNNOT01), 2610262F6 (LUNGUTUT08), 2610262H1 (LUNGUTUT08)
20	86	2700075	OVARUTUT10	604199R1 (BRSTTUT01), 1225126R1 (COLNTUT02), 1923323R6 (BRSTTUT01), 2301778R6 (BRSTNOT05), 2506882F6 (CONUTUT01), 2700075F6 (OVARUTUT10), 2700075H1 (OVARUTUT10), 2744960F6 (LUNGUTUT11), 2833994F6 (TLYMNOT03), 2915413H1 (THYMFET03), 3647274H1 (ENDINOT01)
21	87	2786701	BRSTNOT13	754370R1 (BRAITUT02), 1426163R6 (BEPINON01), 1850667F6 (LUNGFET03), 1923562R6 (BRSTTUT01), 2215161F6 (SINTFET03), 2215161T6 (SINTFET03), 2498589H1 (ADRETUT05), 2991672F6 (KIDNFET02), 3028991H1 (HEARFET02), 3729514H1 (SMCCNON03), 5065467H1 (ARTFTDT01)
22	88	3068538	UTRSNOR01	908465R2 (COLNNOT09), 957130R6 (KIDNNOT05), 1301520F6 (BRSTNOT07), 1580628H1 (DUODNOT01), 2631247F6 (COLNTUT15), 3068538H1 (UTRSNOR01), 3532286T6 (KIDNNOT25)
23	89	5159072	BRSTTMT02	412241R1 (BRSTNOT01), 660435H1 (BRAINOT03), 881160H1 (THYRNOT02), 1304119F6 (PLACNOT02), 1324073F1 (LPARNOT02), 2520427H1 (BRAITUT21), 5159072H1 (BRSTTMT02)



Table 1 (cont.)

Protein SEQ ID NO:	Nucleotide SEQ ID NO:	Clone ID	Library	Fragments
24	90	5519057	LIVRDIR01	066809H1 (HUVESB01), 3279230H1 (STOMFET02), 5370305F6 (BRAINOT22), 5508943F6 (BRADDIR01), 5508943R6 (BRADDIR01), 5519057H1 (LIVRDIR01)
25	91	035379	HUVENOB01	035379H1 (HUVENOB01), 035379X11 (HUVENOB01), 035379X12 (HUVENOB01), 035379X13 (HUVENOB01), 035379X311D1 (HUVENOB01), 112161R1 (PITUNOT01), 1922877R6 (BRSTTUT01), 2133108F6 (ENDCNOT01), 3107232H1 (BRSTTUT15), 4798135H1 (LIVRTUT09), SCHA01519V1, g1802757
26	92	275354	TESTNOT03	275354H1 (TESTNOT03), 275354X1 (TESTNOT03), 1663122T6 (BRSTNOT09), 2104284R6 (BRAITUT02), 2738788T6 (OVARNOT09), 3584082T6 (293TF4T01), SCGA07807V1
27	93	311658	LUNGNOT02	207452X12 (SPLNNOT02), 238306X85F1 (SINTNOT02), 264489H1 (HNT2AGT01), 311658H1 (LUNGNOT02), 1292829F6 (PGANNOT03), 1298271F1 (BRSTNOT07), 1488285H1 (UCMCL5T01), 2555757H1 (THYMNOT03), 2665984F6 (ADRENOT08), 2665984T6 (ADRENOT08), 3079209H1 (BRAIUNT01)
28	94	1251632	LUNGFET03	1251632H1 (LUNGFET03), 1251632X11 (LUNGFET03), 1251632X13 (LUNGFET03), 1316814T1 (BLADTUT02), 1384212F1 (BRAITUT08), 1711274F6 (PROSNOT16), 3128230H1 (LUNGUT12), 4819602H1 (PROSTUT17), SZZZ00620R1
29	95	1331955	PANCNOT07	1363667X12 (LUNGNOT12), 1363667X13 (LUNGNOT12), SBBA01489F1, SBBA01528F1
30	96	1412614	BRAINOT12	1412614F6 (BRAINOT12), 1412614H1 (BRAINOT12), 2278130H1 (PROSNON01), 2278130T6 (PROSNON01), 5105388T6 (PROSTUS19)
31	97	1750781	LIVRTUT01	452712T6 (TLYMNOT02), 483862R6 (HNT2RAT01), 777729R6 (COLNNOT05), 1394724F1 (THYRNOT03), 1652134F6 (PROSTUT08), 1750781F6 (LIVRTUT01), 1750781H1 (LIVRTUT01), 1750781X305F1 (LIVRTUT01), 1750781X307D2 (LIVRTUT01), 3221477H1 (COLNNON03), SCHA02984V1, SXAA02156D1, SXAA00802D1
32	98	1821658	GBLATUT01	909674H1 (STOMNOT02), 1579095F1 (DUODNOT01), 1821658H1 (GBLATUT01), 1821658T6 (GBLATUT01), 2508922F6 (CONUTUT01), 2584263H1 (BRAITUT22), 5571821H1 (TLYMNOT08)
33	99	1872574	LEUKNOT02	305990F1 (HEARNOT01), 908252R2 (COLNNOT09), 1872574H1 (LEUKNOT02), 2051868F6 (LIVRFET02), 2285632R6 (BRAINON01), 3181732F6 (TLYJNOT01), 3285854F6 (HEAONOT05), 3332012H1 (BRAIFET01), SBWA02751V1, SBWA02849V1, SBWA04744V1, SBWA00180V1

Table 1 (cont.)

Protein SEQ ID NO:	Nucleotide SEQ ID NO:	Clone ID	Library	Fragments
34	100	2590967	LUNGNOT22	1340471F6 (COLNTUT03), 2590967F6 (LUNGNOT22), 2590967H1 (LUNGNOT22), 2771160F6 (COLANOT02), 3150287R6 (ADRENON04)
35	101	2824491	ADRETUT06	1381834X14 (BRAITUT08), 1381834X16 (BRAITUT08), 1381834X17 (BRAITUT08), 1381834X31 (BRAITUT08), 1972345F6 (UCMCL5T01), 2824491H1 (ADRETUT06), 3413970H1 (PTHYNOT04)
36	102	2825460	ADRETUT06	870873R6 (LUNGAST01), 1440326F1 (THYRN0T03), 2825460H1 (ADRETUT06), 2825460T6 (ADRETUT06), 4154518H1 (MUSLTM01), 5068209H1 (PANCNOT23), SBLA03097F1
37	103	2871116	THYRN0T10	357664R6 (PROSNOT01), 1419595F1 (KIDNNOT09), 1419595T1 (KIDNNOT09), 1577877F6 (LNODNOT03), 1577877T1 (LNODNOT03), 2767635H1 (COLANOT02), 2871116F6 (THYRN0T10), 2871116H1 (THYRN0T10), 4650546H1 (PROSTUT20), SBHA03160F1, SBHA02613F1, SBHA02703F1
38	104	2942212	CONNTUT05	1270807H1 (TESTTUT02), 1270807X301D1 (TESTTUT02), 1270807X309D2 (TESTTUT02), 2942212H2 (CONNTUT05), g1924758
39	105	3685151	HEAANOT01	860843R1 (BRAITUT03), 1932207F6 (COLNNOT16), 1932207T6 (COLNNOT16), 2210580F6 (SINTFET03), 3043060H1 (HEAANOT01), 3685151H1 (HEAANOT01), 4960825H1 (TLYMNOT05)
40	106	4881515	UTRM0T01	925415R1 (BRAINOT04), 1337450F6 (COLNNOT13), 1961288R6 (BRSTNOT04), 3581069H1 (293TF3T01), 3583842T6 (293TF4T01), 4881515H1 (UTRM0T01), 5488514H1 (DRGTN0N04), g1156606
41	107	5324681	FIBPFEN06	2455960T6 (ENDANOT01), 2458281F6 (ENDANOT01), 3834084F6 (PANCNOT17), 4046332H1 (LUNGNOT35), 5324681H1 (FIBPFEN06), g1733388, g1522074
42	108	5387651	BRAINOT19	810934T1 (LUNGNOT04), 822997R1 (KERANOT02), 1282647F1 (COLNNOT16), 1282647T1 (COLNNOT16), 1571430T6 (UTRSNOT05), 2208839F6 (SINTFET03), 2844787H1 (DRGLN0T01), 2908748H1 (THYMN0T05), 5387651H1 (BRAINOT19)
43	109	5595679	COLCDIT03	044292R6 (TLYN0T01), 826501R1 (PROSNOT06), 1251632X12 (LUNGFET03), 1303934F1 (PLACNOT02), 1316814F1 (BLADTUT02), 1339567T1 (COLNTUT03), 2806159H1 (BLADTUT08), 2837021H1 (TLYMNOT03), 3037493H1 (BRSTNOT16), 3119883H1 (LUNGNOT13), 3395946H1 (LUNGNOT28), 3748742H1 (UTRSNOT18)
44	110	5782457	BRAXNOT03	532593R6 (BRAINOT03), 532593T6 (BRAINOT03), 5782457H1 (BRAXNOT03)

Table 1 (cont.)

Protein SEQ ID NO:	Nucleotide SEQ ID NO:	Clone ID	Library	Fragments
45	111	760677	BRAITUT02	745006X13 (BRAITUT01), 760677H1 (BRAITUT02), 760677X19 (BRAITUT02), 763135X12 (BRAITUT02), 946075H1 (RATRN02), 953938H1 (SCORN001)
46	112	1348567	PROSN011	1348567H1 (PROSN011), 1505075F6 (BRAITUT07), 1620627F6 (BRAITUT13), 2069105F6 (ISLTN01), 2417901F6 (HNT3AZT01), 2494683H1 (ADRETUT05), 3320166H1 (PROSBPT03)
47	113	1751354	LIVRTUT01	029909F1 (SPLNFET01), 029909R1 (SPLNFET01), 512371H1 (MPHGNOT03), 1439362F6 (PANCNOT08), 1751354F6 (LIVRTUT01), 1751354H1 (LIVRTUT01), 1900168F6 (BLADTUT06)
48	114	1976780	PANCUTUT02	001347H1 (U937NOT01), 1755035X307D2 (LIVRTUT01), 1976780H1 (PANCUTUT02), 2798389H1 (NPOLNOT01), 4050076H1 (SINTNOT18), 4228943H1 (BRAMDIT01), 4291877H1 (BRABDIR01), 5514957H1 (BRABDIR01), SCHA04173V1, SCHA02986V1, SCHA01162V1, SCIA02096V1
49	115	2048234	LIVRFET02	1553355F6 (BLADTUT04), 1929455F6 (COLNTUT03), 2048234H1 (LIVRFET02), 2699864T6 (OVRTUT10)
50	116	2111754	BRAITUT03	1335055F6 (COLNNOT13), 2105233R6 (BRAITUT03), 2111754H1 (BRAITUT03), 2111754R6 (BRAITUT03), 3706377H1 (PENCNOT07)
51	117	2123286	BRSTNOT07	411359F1 (BRSTNOT01), 411359R1 (BRSTNOT01), 708105R6 (SYNORAT04), 1322780F6 (BLADNOT04), 2123286H1 (BRSTNOT07), 2719651F6 (LUNGUTUT10), 2880143F6 (UTRSTUT05), 3206153F6 (PENCNOT03), 3210501F6 (BLADNOT08), 3346625F6 (BRAITUT24), 3489118H1 (EPIGNOT01), 3605764H1 (LUNGNOT30), 4242993H1 (SYNWDIT01), 5089472H1 (UTRSTMR01)
52	118	2477507	SMCANOT01	488096H1 (HNT2AGT01), 1672690F6 (BLADNOT05), 1802830F6 (COLNNOT27), 1818538H1 (PROSNOT20), 2171841H1 (ENDCNOT03), 2477507H1 (SMCANOT01), 3434030F6 (PENCNOT05)
53	119	2759119	THP1AZS08	496782H1 (HNT2NOT01), 1251166H1 (LUNGFET03), 1289067F1 (BRAINOT11), 1295658T6 (PGANNOT03), 1510901F1 (LUNGNOT14), 1531583F1 (SPLNNOT04), 1533488F1 (SPLNNOT04), 1817447H1 (PROSNOT20), 2154846F6 (BRAINOT09), 2468875H1 (THYRN0T08), 2498852F6 (ADRETUT05), 2506652F6 (CONUTUT01), 2630812F6 (COLNTUT15), 2759119H1 (THP1AZS08), 2991227H1 (KIDNFET02), 3036646F6 (PENCNOT02), 3213032H1 (BLADNOT08)
54	120	2823818	ADRETUT06	618671R6 (PGANNOT01), 2823818H1 (ADRETUT06), 2950988F6 (KIDNFET01), 31679455

Table 1 (cont.)

Protein SEQ ID NO:	Nucleotide SEQ ID NO:	Clone ID	Library	Fragments
55	121	2859730	SININOT03	103901X6 (BMARNOT02), 510695H1 (MPHGNOT03), 1452088H1 (PENITUT01), 1527095F6 (UCMCL5T01), 2285371H1 (BRAINON01), 2843029H1 (DRGLNOT01), 2859730H1 (SININOT03)
56	122	2861155	SININOT03	875215T1 (LUNGAST01), 999673H1 (KIDNTUT01), 1425091R6 (BEPINON01), 2861155F6 (SININOT03), 2861155H1 (SININOT03), 2901915F6 (DRGCNOT01), 3621947H2 (ENDANOT03)
57	123	3002667	TYMNOT06	227882F1 (PANCNOT01), 227882R1 (PANCNOT01), 260725H1 (HNT2RAT01), 1432542R1 (BEPINON01), 2474761F6 (SMCANOT01), 3002667H1 (TYMNOT06), 3188977H1 (THYMNON04), 3461163H1 (293TFIT01), 4860339F6 (PROSTUT09)
58	124	3043734	HEAANOT01	3043734H1 (HEAANOT01), 3043734T6 (HEAANOT01), 3209823H1 (BLADNOT08), 5277071H1 (MUSLNOT01)
59	125	3294893	TYLJINT01	389234H1 (THYMNOT02), 1242886H1 (LUNGNOT03), 1539958T1 (SINTTUT01), 1870567H1 (SKINBIT01), 2069284F6 (ISLTNOT01), 2280217R6 (PROSNON01), 2353465T6 (LUNGNOT20), 2798990F6 (NPOLNOT01), 3180440H1 (TYLJNOT01), 3294893H1 (TYLJINT01), 3816962H1 (TONSNOT03), 5039889H2 (COLHTUT01), 5118831H1 (SMCBUNT01)
60	126	3349052	BRAITUT24	731775H1 (LUNGNOT03), 1449575H1 (PLACNOT02), 1899442F6 (BLADTUT06), 1967162T6 (BRSTNOT04), 2630025F6 (COLNTUT15), 2717821H1 (THYRNOT09), 3180478T6 (TYLJNOT01), 3349052H1 (BRAITUT24), 4523961F6 (HNT2TXT01), 5565623H1 (TYMNOT08), 6141909H1 (BMARTXT03)
61	127	3357264	PROSTUT16	2378150F6 (ISLTNOT01), 2378150X304B1 (ISLTNOT01), 2378150X304D1 (ISLTNOT01), 2807493F6 (BLADTUT08), 2881251F6 (UTRSTUT05), 3357264F6 (PROSTUT16), 3357264H1 (PROSTUT16), 3593272H1 (293TF5T01), 4163652T6 (BRSTNOT32), 4821588F6 (PROSTUT17), 4872125H1 (COLDNOT01)
62	128	3576329	BRONNOT01	1444072F6 (THYRNOT03), 1649584T6 (PROSTUT09), 1720770X15C1 (BLADNOT06), 1720770X16C1 (BLADNOT06), 2204612F6 (SPLNFET02), 3576329H1 (BRONNOT01), SAFC01083F1
63	129	3805550	BLADTUT03	1416364F6 (BRAINOT12), 1553473H1 (BLADTUT04), 3232384H1 (COLNUCT03), 3287257H1 (HEAONOT05), 3539473H1 (SEMVNOT04), 3805550H1 (BLADTUT03)

Table 1 (cont.)

Protein SEQ ID NO:	Nucleotide SEQ ID NO:	Clone ID	Library	Fragments
64	130	4546403	COLXTDT01	1687704F6 (PROSTUT10), 1962744R6 (BRSTNOT04), 2674742F6 (KIDNNOT19), 4546403H1 (COLXTDT01), 4632828T6 (GBLADIT02)
65	131	4767318	BRATNOT02	134566R1 (BMARNOT02), 549352R1 (BEPINOT01), 1819757T6 (GBLATUT01), 2863295H1 (KIDNNOT20), 4767318H1 (BRATNOT02), SBLA03778F1, g3737930
66	132	4834527	BRAWNOT01	859906X38C1 (BRAITUT03), 1231225H1 (BRAITUT01), 1393681T6 (THYRNUT03), 1416996F6 (BRAINOT12), 2422475H1 (SCORNON02), 3999137R6 (HNT2AZS07), 4834527F6 (BRAWNOT01), 4834527H1 (BRAWNOT01), 5691642H1 (BRAWNOT02)

Table 2

SEQ ID NO:	Amino Acid Residues	Potential Phosphorylation Sites	Potential Glycosylation Sites	Signature Sequences, Motifs, and Domains	Homologous Sequences	Analytical Methods & Databases
1	269	S59 T71 T146 T211 T73 S127 T133 S216	N12	GTP-binding protein: D79-M234, Y80-C239 ATP/GTP binding site (P-loop): G102-S109	GTP-binding protein; Cgpa [Caulobacter crescentus] g3820578	BLAST-Genbank BLAST-DOMO MOTIFS
2	428	S59 S188 S200 S284 S367 S381 T399 T29 T193 T288 T354 S419		Beta transducin family, G-beta repeats: T269-L315, F261-D293 L280-V294, V185-V199 Signal peptide: M1-A35		ProfileScan MOTIFS BLIMPS-PRINTS HMMER-PFAM SPScan
3	562	S151 S152 T443 T444 S33 S104 S126 S127 S135 S216 S239 T350 T383 S450 T481 S146 T223 S287 S356 T434 T470 Y501	N125 N354 N445		Ras inhibitor [Homo sapiens] g190895	BLAST-Genbank
4	229	T108 S153 S9 S160 S215 T219 T142 S180	N111 N140 N198	ATP/GTP-binding site: G28-S35 Ras family: K23-T219 Ras transforming protein: V22-M43, A63-S85, P124-A137, L156-A178, D102-S145, K150-S180	Small GTP binding protein [Saccharomyces cerevisiae] g1171484	BLAST-Genbank MOTIFS HMMER-PFAM BLIMPS-BLOCKS BLIMPS-PRINTS BLAST-DOMO
5	360	T108 S360 S115 T217 T264 S295 S296 S35 S52 S160 S174 T206 T249	N149 N287 N327 N351	WD domain, G-beta repeats: M1-T64, M27-K41, F274-K306	Similar to WD domain, G-beta repeat protein [C. elegans] g3880929	BLAST-Genbank HMMER-PFAM ProfileScan BLIMPS-PRINTS
6	460	T18 T107 T123 S149 S199 S280 S336 S369 S71 T106 S387 Y302 Y400	N270 N350	Signal peptide: M1-A57	Rabin3 [Rattus norvegicus] g624225	BLAST-Genbank SPScan

Table 2 (cont.)

SEQ ID NO:	Amino Acid Residues	Potential Phosphorylation Sites	Potential Glycosylation Sites	Signature Sequences, Motifs, and Domains	Homologous Sequences	Analytical Methods & Databases
7	239	S234 S25 T47 T52 S98 T190 T206 S236 S223	N188	Phosducin: L20-I179, S25-I179, E30-D239	Phosducin-like protein [Homo sapiens] g4104075	BLAST-Genbank BLAST-PRODOM BLAST-DOMO
8	334	T225 T235 S260 T4 S45 S63 S133 S162 S193 T279 T308		ATP/GTP-binding site (P-loop): G150-S157 GTP1/OBG family: L75-D89, I146-Q166 G-protein, alpha subunit: I79-L87	GTP-binding protein homolog [L. braziliensis] g2570231	BLAST-Genbank MOTIFS BLIMPS-BLOCKS BLIMPS-PRINTS
9	341	S91 T122 S185 T199 T228 S65 T85 S323		Signal peptide: M1-A61 WD domain, G-beta repeats: L164-D196, C173-P217, V183-L197, S185-W195	Putative WD-40 repeat protein [Arabidopsis thaliana] g4191773	SPScan BLAST-Genbank MOTIFS ProfileScan HMMER-PFAM BLIMPS-BLOCKS BLIMPS-PRINTS
10	513	T29 T72 T109 S124 S136 S215 T341 T481 T501 S65 T245 T330 S338 T372 T386 S437 S451 T473 Y228 Y254	N242 N417	Beta-transducin family, G-beta repeats: F345-N377, K210-N242, E303-G335, S366-W376, N353-V400, L229-F243, I364-M378	Similar to WD domain G-beta repeats protein [C. elegans] g3875246	BLAST-Genbank MOTIFS HMMER-PFAM BLIMPS-BLOCKS BLIMPS-PRINTS ProfileScan
11	186	T61 S80 S107 S163 S31 T66 S183	N64 N148	ARF-family: N6-S186, P51-S90, M95-L149 GTP-binding, SAR1 protein: F78-K103, I123-I144 ATP/GTP binding site (P-loop): G27-T34	Similar to ADP- ribosylation factor [C. elegans] g3881189	BLAST-Genbank HMMER-PFAM BLIMPS-BLOCKS BLIMPS-PRINTS MOTIFS

Table 2 (cont.)

SEQ ID NO:	Amino Acid Residues	Potential Phosphorylation Sites	Potential Glycosylation Sites	Signature Sequences, Motifs, and Domains	Homologous Sequences	Analytical Methods & Databases
12	204	S184 S203 S34 S152 T14 T20 T25 T62 S86		Ras family: K5-M189 Ras transforming protein: M1-E150, V4-T25, V113-L126 ATP/GTP binding site (P-loop): G10-S17	Ras-like protein, rit [Mus musculus] g1656005	BLAST-Genbank HMMER-PFAM BLIMPS-PRINTS BLAST-DOMO MOTIFS
13	100	S31 S46 T52 T61 S84 S4 S26 S27 T86		Beta-transducin, WD repeats: L81-M95, V70-S100, M1-S100	Similar to beta-transducin [C. elegans] g3875373; Alzheimer's disease protein [Homo sapiens] GeneSeq W21578	BLAST-Genbank MOTIFS BLIMPS-BLOCKS ProfileScan BLIMPS-PRINTS BLAST-PRODOM
14	795	T569 S776 S54 S188 S201 T248 T249 T298 S306 S368 T422 S466 T561 S586 S625 S678 T731 S777 S13 T42 S120 T134 T174 S213 S254 T266 S391 S415 S588 S620 S694 T742	N52 N421 N559 N585 N708	WD domain, G-beta repeats: L108-L139, L147-K179, T168-W178, Y227-K259, L126-N140, M166-A180	Phospholipase A2-activating protein [Rattus Norvegicus] g1017706	BLAST-Genbank BLAST-PRODOM BLAST-DOMO HMMER-PFAM BLIMPS-BLOCKS BLIMPS-PRINTS
15	393	S48 S61 T143 T334 T148 T200 S208 T212 T245 S266 S325	N182 N197	WD domain, G-beta repeats: L121-A153, L357-R389, P322-F369, L140-S154	Putative WD-repeat protein [Arabidopsis thaliana] g4263521	BLAST-Genbank HMMER-PFAM ProfileScan BLIMPS-PRINTS
16	485	S31 S108 S222 S321 S346 S357 T84 T125 T137 T151 T187 S227 T268 S395 T403 S409 T437 Y92 Y261		Beta-transducin, WD repeats: L129-L143, V219-T233, S262-W272, V387-G401, L429-V443, L452-G468	Notchless protein [Xenopus laevis] g3687833	BLAST-Genbank MOTIFS HMMER-PFAM ProfileScan BLIMPS-BLOCKS BLIMPS-PRINTS BLAST-DOMO BLAST-PRODOM



Table 2 (cont.)

SEQ ID NO:	Amino Acid Residues	Potential Phosphorylation Sites	Potential Glycosylation Sites	Signature Sequences, Motifs, and Domains	Homologous Sequences	Analytical Methods & Databases
17	199	T32 T91 S177 T56 S153 S186 Y149		ATP/GTP-binding site (P-loop): G15-T22 Transforming protein, p21: L9-H30, T32-K48, I50-S72, Q115-L128, Y149-A171 Ras protein: K5-E151	Rab7 [Mus musculus] g1050551	BLAST-Genbank MOTIFS BLIMPS-PRINTS BLAST-PRODOM BLAST-DOMO
18	163	T18 T46 S120 S5 T151 T83 S125	N81 N159		Rhotekin [Mus musculus] g1293145	BLAST-Genbank
19	290	S56 S84 T234 S41 T91 T132 T234 T11 T47 T80 T194	N89 N188	Beta-transducin, WD-repeats: S41-W51, F195-D227, L238-N270, L214-I228, L257-M271, T203-S249	Similar to beta-transducin; [C. elegans] g3875373; Alzheimer's disease protein [Homo sapiens] GeneSeq W21578	BLAST-Genbank MOTIFS HMME-PFAM BLIMPS-BLOCKS ProfileScan BLIMPS-PRINTS BLAST-PRODOM
20	705	T277 T364 S393 S448 S479 S483 T554 T568 S586 S239 S250 T374 S379 T398 S485 T528	N274	Beta-transducin, WD-repeats: L390-L404, L370-D403, L413-R445	Similar to WD domain G-beta repeat prot. [C. elegans] g3880340; 70kD tumor-specific antigen [R. norvegicus] g2505957	BLAST-Genbank HMME-PFAM BLAST-PRODOM BLAST-DOMO BLIMPS-BLOCKS BLIMPS-PRINTS MOTIFS
21	454	T426 S451 S28 S51 T81 T89 T166 S214 T241 S264 T305 S343 S185 T193 S421	N58	ATP/GTP-binding site (P-loop): G73-S80 Cell division control protein: V47-P240	Similar to Drosophila melanogaster septin (sep2) [Homo sapiens] g1503988	BLAST-Genbank BLAST-PRODOM BLAST-DOMO MOTIFS
22	433	S169 T239 T292 S309 S382 S129 S297 Y60 Y101 Y315	N338	Protein GTPase activating protein: L8-S169 PH domain: Y138-Q355, Q191-I351, P210-E375	RhoGAP protein [Homo sapiens] g312212	BLAST-Genbank BLAST-PRODOM BLAST-DOMO

Table 2 (cont.)

SEQ ID NO:	Amino Acid Residues	Potential Phosphorylation Sites	Potential Glycosylation Sites	Signature Sequences, Motifs, and Domains	Homologous Sequences	Analytical Methods & Databases
23	406	T83 S143 S303 T75 T115 T126 T211 S216 T289 T315 Y247	N184 N401 N402		Rab 9 effector, P40 [Homo sapiens] g2217970	BLAST-GenBank
24	229	S7 S127 T50 S178		ATP/GTP-binding site (P-loop): G40-T47 Ras family: K35-L217 Transforming protein, p21: F34-A55, R57-R73, V75-K97, N139-L152	Rab GTPase, Rab33B [Mus musculus] g2516239	BLAST-GenBank MOTIFS HMMER-PFAM BLIMPS-PRINTS BLAST-DOMO
25	670	T28 T45 S69 S3 S108 T277 S406 S6 T52 T82 S91 S102 S126 S609 S158 S197 T213 S217 T281 S323 S416 T419 T428 T474 S496 T540 S624 T664	N343	G-beta WD repeat domain: F386-D424, L411-T425, Y429-D465, L469-D504, L510-D545, L549-D585, K589-S629, M633-T669 Beta-transducin Trp-Asp repeats signature: C401-I447	Beta transducin- like protein [Podospira anserina] g607003	BLAST-GenBank BLIMPS-BLOCKS BLIMPS-PRINTS HMMER-PFAM MOTIFS ProfileScan
26	445	T17 T48 T126 T160 T293 T364 T97 T132 S201 S217 S305 T322 S357 S434 Y339	N46 N95 N355	G-beta WD repeat domain: L62-N95, V82-L96, F124-M138, F297-V311 Beta-transducin Trp-Asp repeats signature: S316-A356 SOF1 protein, WD repeat: D129-V277, F309-V444	Beta-transducin [Schizosaccharomyces pombe] g3393019	BLAST-GenBank BLAST-DOMO BLAST-PRODOM BLIMPS-BLOCKS BLIMPS-PRINTS HMMER-PFAM MOTIFS
27	236	S24 S60 S86 T181 S117 S140		GYP7, GTPase activating protein: M1-I155	GTPase activating protein [Yarrowia lipolytica] g2370595	BLAST-GenBank BLAST-PRODOM MOTIFS

Table 2 (cont.)

SEQ ID NO:	Amino Acid Residues	Potential Phosphorylation Sites	Potential Glycosylation Sites	Signature Sequences, Motifs, and Domains	Homologous Sequences	Analytical Methods & Databases
28	498	S97 T158 S247 S281 S425 S468 S494 T84 S176 T355 T474 Y239		G-beta WD repeat domain: L188-Q220, L446-G479, M466-P480 Beta-transducin Trp-Asp repeats signature: F200-A245	Similarity to guanine nucleotide binding protein [Caenorhabditis elegans] g3878300	BLAST-GenBank BLIMPS-BLOCKS BLIMPS-PRINTS HMMER-PFAM MOTIFS ProfileScan
29	334	S63 S104 S148 S189 T208 S276 S50 T110 S118 T124 S152 T160 T237 T326	N265	G-beta WD repeat domain: L41-G73, I83-D115, L102-V116, L125-D157, L167-D199, I210-D242 Beta-transducin Trp-Asp repeats signature: S49-A308 Signal peptide: M1-A47	Similar to guanine nucleotide binding protein [Caenorhabditis elegans] g3874290	BLAST-GenBank BLAST-PRODOM BLIMPS-BLOCKS BLIMPS-PRINTS HMMER-PFAM MOTIFS ProfileScan SPScan
30	292	S102 T145 S188 S52 T89 S204 S222 S283	N209	Protein with WD repeat: P7-W129 Signal peptide: M1-S68	F-box protein FBX16 [Mus musculus] g6456114	BLAST-PRODOM BLAST-GenBank MOTIFS SPScan
31	588	T184 T76 T137 S139 T161 T174 T183 S285 T351 T375 S432 T473 S488 S213 T265 S389 S394 T412 T546	N159	G-beta WD repeat domain: A293-E331, C337-T375, Y379-D417, I404-L418, E460-D497, T506-S543, G547-A586 Beta-transducin Trp-Asp repeats signature: A308-E354, L393-Q441	TipD (sequence similarity to Beta-transducin family) [Dictyostelium discoideum] g2407788	BLAST-GenBank BLAST-PRODOM BLIMPS-BLOCKS BLIMPS-PRINTS HMMER-PFAM MOTIFS ProfileScan
32	326	T50 T84 S98 S142 T261 T65 T148 T178 T189 T221	N187	G-beta WD repeat domain: L120-N153, I140-L154		BLIMPS-BLOCKS BLIMPS-PRINTS HMMER-PFAM MOTIFS
33	453	T157 T218 T248 S320 S347 S412 S7 T236 S290 T396 T406 Y63	N59 N225	G-beta WD repeat domain: D180-E211, A198-V212		BLIMPS-BLOCKS BLIMPS-PRINTS HMMER-PFAM MOTIFS

Table 2 (cont.)

SEQ ID NO.	Amino Acid Residues	Potential Phosphorylation Sites	Potential Glycosylation Sites	Signature Sequences, Motifs, and Domains	Homologous Sequences	Analytical Methods & Databases
34	161	T137 T18 T102 Y96		DMR-N9 protein: K93-S148	DMR-N9 (homology to WD repeat sequences) [Mus musculus] g817954	BLAST-GenBank BLAST-PRODOM MOTIFS
35	684	T173 S25 S43 S74 S83 S127 S152 S154 S182 T316 T331 T341 S372 T535 T606 S623 T138 T151 S168 S238 S299 T336 T422 S476 T506 T530 T628 T647	N526 N621	ATP/GTP-binding site motif A (P-loop): G267 Elongation factor 1 alpha protein (GTP-binding) domain: D485-E684 Elongation factor Tu domain: K258-D658, N262-K273, M343-G374, R664-G677 GTP-binding elongation factors signature: A249-E420, N262-T275, K294-P346, T341-F351, T357-V368, L401-Q410, P443-I682 RAS transforming protein: K258-V439	eRFs (related to eukaryotic release factor 3) [Mus musculus] g4566435	BLAST-GenBank BLAST-DBO BLAST-PRODOM BLIMPS-BLOCKS BLIMPS-PRINTS HMMER-PFAM MOTIFS ProfileScan
36	366	S342 T52 S71 T102 T119 T224 T324 T66 S195 S271 T353 Y225	N32	G-beta WD repeat domain: V146-L160, L284-I298 Signal Peptide: M1-T56		BLIMPS-PRINTS MOTIFS SPScan
37	339	S152 S183 T107 T115		Beta-transducin Trp-Asp repeats signature: N101-L162 Trp-Asp repeats-containing protein: R54-A172 Transmembrane domain: A300-I323	Hypothetical trp-asp repeats containing protein [Schizosaccharomyces pombe] g3850059	BLAST-GenBank BLAST-DBO BLAST-PRODOM HMMER MOTIFS

Table 2 (cont.)

SEQ ID NO:	Amino Acid Residues	Potential Phosphorylation Sites	Potential Glycosylation Sites	Signature Sequences, Motifs, and Domains	Homologous Sequences	Analytical Methods & Databases
38	213	T29 T134 S153 T181 S200 T92 T129 S207		ATP/GTP-binding site motif A (P-loop): G15 GTP-binding protein signature (Arf1, Ran): W5-E179 Ras family signature: R10-C213 Transforming protein p21: F9-E30, R32-R48, E51-S73, Y114-L127, Y149-I171 Signal peptide: M1-V19	Rab-related GTP-binding protein [Homo sapiens] g1491714	BLAST-GenBank BLAST-DOMO BLAST-PRODOM BLIMPS-PRINTS HMMER-PFAM MOTIFS SPScan
39	393	S209 T363 S60 S99 S119 S135 T144 T147 S174 S210 T350 S359 S370 T371		G-beta WD repeat domain: G33-D69, K73-D110, L97-A111, W114-N152, L236-K276, I263-L277 signal peptide: M1-T43	Similar to beta-transducin [Caenorhabditis elegans] g860695	BLAST-GenBank BLIMPS-BLOCKS BLIMPS-PRINTS HMMER-PFAM MOTIFS SPScan
40	399	S86 T191 S219 S224 S254 S275 S308 S59 S72 T96 S373 S385 T394	N88 N106 N321 N322	ATP/GTP-binding site motif A (P-loop): G68 G-protein alpha subunit: R63-Q78 GTP-binding protein GTR1: A57-D294 Ras transforming protein: K61-L203	Gtr2 homolog, novel small GTPase subfamily [Schizosaccharomyces pombe] g3560242	BLAST-GenBank BLAST-DOMO BLAST-PRODOM BLIMPS-PRINTS MOTIFS
41	412	T106 S337 S391 S29 S30 S41 S130 S154 S207 S231 S326 S82 S97 T212 S220	N367	G-beta WD repeat domain: C184-E217, L204-Y218 signal peptide: M1-G18	Putative transcriptional regulation protein, trp-asp repeat containing [Schizosaccharomyces pombe] q3766375	BLAST-GenBank BLIMPS-BLOCKS BLIMPS-PRINTS HMMER-PFAM MOTIFS SPScan

Table 2 (cont.)

SEQ ID NO:	Amino Acid Residues	Potential Phosphorylation Sites	Potential Glycosylation Sites	Signature Sequences, Motifs, and Domains	Homologous Sequences	Analytical Methods & Databases
42	163	S15 S17 S71 T114 Y49			Arf-like 2 binding protein BART1 [Homo sapiens] g4426962	BLAST-GenBank MOTIFS
43	514	S113 T174 S263 S297 S441 S484 S510 T100 S192 T371 T490 Y255		G-beta WD repeat domain: L204-Q236, L462-G495, M482-P496 Beta-transducin Trp-Asp repeats signature: F216-A261	Similarity to guanine nucleotide binding protein [Caenorhabditis elegans] g3878300	BLAST-GenBank BLIMPS-BLOCKS BLIMPS-PRINTS HMMER-PFAM MOTIFS ProfileScan
44	67	T30 S15 Y18		G-protein gamma subunit: E2-L67, M9-R24, K10-P57, D45-G62 Prenyl group binding site (CAAX box): V64	G gamma protein [Mus musculus] g7259257	BLAST-GenBank BLIMPS-BLOCKS BLIMPS-PRINTS HMMER-PFAM MOTIFS
45	315	T148 S162 S209 S244 S252 S45 T48 S132 S140 S158 T214 S244	N79	WD40 domains/G-beta repeats: Q15-N53, G57-N95, G99-D137, P143-D179, G223-D263 WD/G-beta profiles: L71-Q116, T114-V161 WD/G-beta repeat signature: V250-L264	Contains similarity to G beta repeats (PROSITE:PS00670) of the beta- transducin family [Caenorhabditis elegans] g1086900	BLAST-GenBank MOTIFS ProfileScan HMMER-PFAM
46	504	T268 T99 T193 S323 S324 T409 T493 T91 T98 T133 T185 T234 T259 T264 T287 T337 S415 S498	N37 N295	WD40 domains/G-beta repeats: A211-D250, E254-S292, A296-A331, G338-D378, R382-D420 WD/G-beta profiles: T396-I442, T268-A316, C355-F400 WD/G-beta signatures: L407-L421, V279-V293 WD repeat protein-like region: I4-A226	Similar to S. cerevisiae PRP19 protein; similar to G-beta repeat region of guanine nucleotide binding protein [Caenorhabditis elegans] g727450	BLAST-GenBank BLAST-PRODROM MOTIFS BLIMPS-PRINTS ProfileScan HMMER-PFAM

Table 2 (cont.)

SEQ ID NO:	Amino Acid Residues	Potential Phosphorylation Sites	Potential Glycosylation Sites	Signature Sequences, Motifs, and Domains	Homologous Sequences	Analytical Methods & Databases
47	522	S84 S315 S510 T20 S50 S57 S74 S116 S122 S128 S161 S185 T274 T300 S339 S345 S357 S367 T373 S459 T474 S136 S143 T174 S200 T300 S315 S356 S385 S420 T492	N226 N355		SAPK (stress activated protein kinase) interacting protein (similar to ras inhibitor) [Gallus gallus] g4929812	BLAST-GenBank MOTIFS
48	316	T109 S27 S86 S188 S7 S8 S82 T96 T105	N29 N136 N186	Pleckstrin homology (PH) domains: S3-N45, I59-Q301 RhoGAP domain: P140-N291 GTPase protein-like region: G125-L307	Beta2-chimaerin [Homo sapiens] g457230	BLAST-GenBank BLAST-PRODOM BLAST-DOMO HMMER-PFAM MOTIFS BLIMPS-PRINTS BLIMPS-PRODOM
49	387	S97 S199 T249 S342 S369 S382 T54 T182 T381		ATP/GTP-binding site motif (P-loop): G155-S162 GTP1/OBG GTP-binding protein family signatures: V151-A171, K172-I190, V200-G215, G217-D235 GTP-binding protein-like region: F15-P173 RAS transforming protein-like region: L145-L296	GTP-binding protein [Aquifex aeolicus] g2984292	BLAST-GenBank BLAST-PRODOM BLAST-DOMO BLIMPS-BLOCKS BLIMPS-PRINTS MOTIFS

Table 2 (cont.)

SEQ ID NO:	Amino Acid Residues	Potential Phosphorylation Sites	Potential Glycosylation Sites	Signature Sequences, Motifs, and Domains	Homologous Sequences	Analytical Methods & Databases
50	334	T228 T308 S65 S91 T224 T228 T262 S34 S81 T224 T262 S286 T324	N108 N257 N322	ATP/GTP-binding site motif (P-loop): G149-S156 Ras domain: R144-M334 p21/ras-related transforming protein signatures: Y143-S164, N166-L182, H248-D261, F282-K304 Ras transforming protein-like region: I140-E284	NOEY2 putative tumor suppressor [Homo sapiens] g94100355	BLAST-GenBank BLAST-PRODOM BLAST-DBO HMMER-PFAM BLIMPS-BLOCKS BLIMPS-PRINTS MOTIFS
51	551	T199 S38 T62 S85 T116 S169 S351 T379 S421 S422 S456 S12 S22 S150 T366 S383 T482 Y404 Y449	N133 N148 N179 N293 N296	Regulator of chromosome condensation (RCC1)/ guanine nucleotide dissociation stimulator domains: E117-S169, D170-D222, T223-D274, E275-G292, G328-G339 RCC1 signatures: V157-L167, V262-L272	UVB-resistance protein UVR8 [Arabidopsis thaliana] g5478530	BLAST-GenBank BLAST-PRODOM HMMER-PFAM PROFILES-SCAN BLIMPS-PRINTS MOTIFS
52	308	S152 T230 S266 S299 S19 S22 S240	N76	WD40 domains/G-beta repeats: Q33-R73, W79-T119, W126-K181, W188-T230, P241-K276, S11-A50 Sec13 related/WD repeat protein-like region: R73-I177 WD/G-beta profile: G11-A50	Sec13-related protein [Arabidopsis thaliana] g3150415	BLAST-GenBank HMMER-PFAM PROFILES-SCAN BLIMPS-PRINTS BLAST-PRODOM MOTIFS



Table 2 (cont.)

SEQ ID NO:	Amino Acid Residues	Potential Phosphorylation Sites	Potential Glycosylation Sites	Signature Sequences, Motifs, and Domains	Homologous Sequences	Analytical Methods & Databases
53	949	S206 S514 T22 S216 T226 S273 T315 S663 T745 T908 T155 S232 S258 T350 S359 S472 S609 S776 S837 S913 Y682 Y862	N114	WD40 domains/G-beta repeats: V199-K237, V248-S284, G287-H326 Drosophila lethal(2) giant larvae tumor suppressor protein signature: K221-P244, A353-E377		HMER-PFAM BLIMPS-PRINTS MOTIFS
54	227	S11 T113 S173 T155 S173	N38	ATP/GTP-binding site motif (P-loop): G37-T44 Ras family domain: K32-C227 p21/ras-related transforming protein signatures: F31-D52, S54-K70, V72-T94, D134-M147, F169-I191 Ras transforming protein-like region: F27-T172	GTP-binding protein [Bos taurus] g162764	BLAST-GenBank HMER-PFAM BLIMPS-PRINTS BLAST-DOMO BLAST-PRODOM MOTIFS
55	474	T430 S98 S118 S309 S450 S463 T66 S130 T141 S241 S289 S309 S389 S450	N179 N185	WD40 domains/G-beta repeats: D70-Q109, T120-N159, E164-D202 G-beta repeat signature: L146-V160 WD repeat/coronin protein-like region: I208-Q467	Coronin-2 [Mus musculus] g4895039	BLAST-GenBank HMER-PFAM BLAST-PRODOM BLAST-DOMO MOTIFS
56	547	S16 T77 S85 S90 S112 S114 T132 S160 T166 T225 S248 S438 S491 S526 S125 S267 T299 T305 S504	N101 N110 N147 N297	WD40 domains/G-beta repeats: G159-N197, C312-A353, G357-D396 WD40/G-beta signatures: V245-A259, L428-T442	Guanine nucleotide-binding protein beta 5 [Mesocricetus auratus] g1001939	BLAST-GenBank HMER-PFAM BLIMPS-PRINTS MOTIFS

Table 2 (cont.)

SEQ ID NO:	Amino Acid Residues	Potential Phosphorylation Sites	Potential Glycosylation Sites	Signature Sequences, Motifs, and Domains	Homologous Sequences	Analytical Methods & Databases
57	686	T331 S431 T637 S34 S169 S554 S28 S124 S192 S273 S341 T366 S426 S449 S470 S15 T2 S3 T24	N26 N44 N271 N424 N628	G-beta profile: S106-S152	Beta-transducin-like protein [Podospira anserina] g607003	BLAST-GenBank PROFILES-SCAN HMMER-PFAM
58	93				HP protein (RhoGAP ortholog) [Homo sapiens] g2559002	BLAST-GenBank MOTIFS
59	521	S63 S223 T64 T117 S147 S159 S195 S200 T214 S271 S401 S448 T49 S110 S195 T235 T280 T439	N71 N108 N381	Amino acyl tRNA ligase motif: P173-T183	GTPase activating protein [Schizosaccharomyces pombe] g3150248	BLAST-GenBank MOTIFS
60	751	T287 S543 T61 S275 S345 T430 T474 T565 T676 S705 S726 T727 S57 T63 T70 T287 S345 T389 T432 S458 T479 T518 T538	N344 N640	GTP binding elongation factor Tu family domain: E44-T530 Elongation factor G C-terminus domain: L556-T727 GTP binding elongation factor signatures: N48-T61, Q97-A105, N117-F127, R133-V144, F169-R178	Elongation factor G [Rattus norvegicus] g310102	BLAST-GenBank HMMER-PFAM BLIMPS-BLOCKS BLIMPS-PRINTS ProfilesScan BLAST-PRODOM BLAST-DOMO MOTIFS
61	666	T492 S615 S619 T35 S142 T177 T212 S224 S270 T353 S403 T456 T471 T500 T550 S560 S572 T378 S403 S496 T509 T608 T611 T625	N75 N582		Rho target rhophilin [Mus musculus] g1176422	BLAST-GenBank MOTIFS

Table 2 (cont.)

SEQ ID NO:	Amino Acid Residues	Potential Phosphorylation Sites	Potential Glycosylation Sites	Signature Sequences, Motifs, and Domains	Homologous Sequences	Analytical Methods & Databases
62	746	S22 T98 S571 T46 S53 S61 S66 S70 S71 T97 S14 S126 S127 T165 T184 T190 S249 S279 S323 S430 S519 S680 S736 S115 T190 T237 S349 S436 T444 S567 S598 S601 T613 S652 T741		WD40 domains/G-beta repeats: T403-E441, R570-H606, Q610-D648, T653-H691, L704-T746, C418-A461 G-beta repeat signature: L428-V442 Trp-Asp repeat protein-like region: S22-L407	Bop1 growth control protein [Mus musculus] g1679772	BLAST-GenBank BLAST-PRODOM BLAST-DOMO MOTIFS BLIMPS-PRINTS ProfileScan HMMER-PFAM
63	212	S105 S142 S148 S162 S167 S44 T56 T101 S162 S190	N131	ATP/GTP-binding site motif (P-loop): G25-T32 Ras family domain: K20-C212 ADP-ribosylation factor family domain: P6-R183 p21/ras-related transforming protein signatures: F19-T40, A42-K58, L60-T82, S122-L135, A158-L180 Ras transforming protein-like region: Y15-I155	Rab19 [Mus musculus] g2598565	BLAST-GenBank HMMER-PFAM BLIMPS-BLOCKS BLIMPS-PRINTS BLAST-DOMO BLAST-PRODOM MOTIFS

Table 2 (cont.)

SEQ ID NO:	Amino Acid Residues	Potential Phosphorylation Sites	Potential Glycosylation Sites	Signature Sequences, Motifs, and Domains	Homologous Sequences	Analytical Methods & Databases
64	307	T275 S276 T15 S25 T99 S164 S201 S6 S270 T293	N196 N291	WD40 domains/G-beta repeats: M1-I49, L60-D98, E102-Q140 Sterile alpha motif (SAM): E161-R225 WD/G-beta signatures: L36-V50, L127-F141 G-beta profile: L74-P122	Hypothetical trp-asp repeats protein [C. elegans] SwissProt Q93847	BLAST-SwissProt HMMER-PFAM BLIMPS-PRINTS ProfileScan MOTIFS
65	378	S137 T167 T193 S202 S237 S276 S290 S310 S362 S82 T150 T158 T199 S362 T368		WD40 domains/G-beta repeats: H72-L110, L116-D155, L241-D279 G-beta profiles: S137-C175, S87-C133, I255-S312	WD repeat protein [Schizosaccharomyces pombe] g5701965	BLAST-GenBank HMMER-PFAM ProfileScan MOTIFS
66	466	S6 T24 S69 T209 S246 S357 T450 S181 S236 S242 T322 T407 T450	N448	RasGEF domain: V197-E397 Guanine nucleotide releasing protein-like region: P201-S432	Putative guanine-nucleotide releasing factor [Drosophila affinis] g2981229	BLAST-GenBank HMMER-PFAM BLAST-PRODOM BLAST-DOMO

Table 3

Nucleotide SEQ ID NO:	Selected Fragments	Tissue Expression (Fraction of Total)	Disease or Condition (Fraction of Total)	Vector
67	434-478	Cardiovascular (0.238) Reproductive (0.238) Hematopoietic/Immune (0.190)	Cancer (0.429) Inflammation/Trauma (0.524) Cell Proliferation (0.095)	pINCY
68	380-424 551-595	Nervous (0.185) Reproductive (0.167) Gastrointestinal (0.148)	Cancer (0.444) Cell Proliferation (0.315) Inflammation/Trauma (0.278)	pINCY
69	433-477	Reproductive (0.429) Nervous (0.142) Hematopoietic/Immune (0.142)	Cancer (0.714) Inflammation/Trauma (0.142)	pINCY
70	684-728	Reproductive (0.333) Nervous (0.178) Cardiovascular (0.111)	Cancer (0.467) Cell Proliferation (0.244) Inflammation/Trauma (0.267)	pINCY
71	219-263	Hematopoietic/Immune (0.257) Reproductive (0.229) Gastrointestinal (0.143)	Cell Proliferation (0.400) Inflammation/Trauma (0.429) Cancer (0.314)	pINCY
72	865-912	Gastrointestinal (0.286) Reproductive (0.286) Cardiovascular (0.238)	Cancer (0.667) Cell Proliferation (0.143) Inflammation/Trauma (0.238)	pINCY
73	900-944	Reproductive (0.229) Hematopoietic/Immune (0.157) Nervous (0.157)	Cancer (0.422) Inflammation/Trauma (0.349) Cell Proliferation (0.205)	pINCY
74	109-153 919-963	Reproductive (0.270) Gastrointestinal (0.162) Cardiovascular (0.135)	Cancer (0.405) Cell Proliferation (0.270) Inflammation/Trauma (0.324)	pINCY
75	1352-1396 1568-1612	Reproductive (0.296) Gastrointestinal (0.167) Nervous (0.167)	Cancer (0.509) Inflammation/Trauma (0.269) Cell Proliferation (0.157)	pINCY
76	541-585 1189-1233	Reproductive (0.238) Cardiovascular (0.190) Gastrointestinal (0.190)	Cancer (0.524) Inflammation/Trauma (0.310) Cell Proliferation (0.143)	PBLUESCRIPT
77	110-154	Reproductive (0.250) Nervous (0.224) Hematopoietic/Immune (0.132) Gastrointestinal (0.132)	Cancer (0.355) Inflammation/Trauma (0.342) Cell Proliferation (0.211)	PSPORT1
78	218-262	Reproductive (0.375) Nervous (0.188) Urologic (0.188)	Cancer (0.562) Inflammation/Trauma (0.250)	pINCY

Table 3 (cont.)

Nucleotide SEQ ID NO:	Selected Fragments	Tissue Expression (Fraction of Total)	Disease or Condition (Fraction of Total)	Vector
79	380-424	Hematopoietic/Immune (0.227) Nervous (0.227) Reproductive (0.227)	Inflammation/Trauma (0.636) Cancer (0.364)	PSPORT1
80	217-261	Reproductive (0.275) Gastrointestinal (0.196) Nervous (0.196)	Cancer (0.431) Inflammation/Trauma (0.451) Cell Proliferation (0.196)	PSPORT1
81	488-532 812-856	Reproductive (0.301) Nervous (0.151) Gastrointestinal (0.130)	Cancer (0.466) Inflammation/Trauma (0.288) Cell Proliferation (0.151)	pINCY
82	595-639	Reproductive (0.333) Developmental (0.148) Gastrointestinal (0.148)	Cancer (0.444) Cell Proliferation (0.370) Inflammation/Trauma (0.333)	pINCY
83	219-263	Hematopoietic/Immune (0.400) Gastrointestinal (0.200) Cardiovascular (0.100)	Inflammation/Trauma (0.429) Cell Proliferation (0.357) Cancer (0.286)	pINCY
84	164-208	Cardiovascular (0.667) Nervous (0.222) Hematopoietic/Immune (0.111)	Cancer (0.556) Cell Proliferation (0.111)	PBLUESCRIPT
85	487-531 757-801	Reproductive (0.182) Cardiovascular (0.091)	Cancer (0.308) Cell Proliferation (0.231) Inflammation/Trauma (0.154)	pINCY
86	325-369 811-855	Hematopoietic/Immune (0.288) Reproductive (0.197) Cardiovascular (0.136)	Inflammation (0.394) Cancer (0.318) Cell Proliferation (0.212)	pINCY
87	163-207	Reproductive (0.218) Nervous (0.172) Gastrointestinal (0.138)	Cancer (0.448) Cell Proliferation (0.218) Inflammation (0.207)	pINCY
88	362-406 758-802	Reproductive (0.273) Gastrointestinal (0.227) Cardiovascular (0.136) Musculoskeletal (0.136)	Cancer (0.681) Cell Proliferation (0.182) Inflammation/Trauma (0.318)	pINCY
89	272-316	Reproductive (0.229) Gastrointestinal (0.193) Nervous (0.193)	Cancer (0.404) Inflammation (0.220) Cell Proliferation (0.165)	pINCY

Table 3 (cont.)

Nucleotide SEQ ID NO:	Selected Fragments	Tissue Expression (Fraction of Total)	Disease or Condition (Fraction of Total)	Vector
90	98-142	Nervous (0.400) Cardiovascular (0.200) Developmental (0.200) Gastrointestinal (0.200)	Cell Proliferation (0.400) Inflammation (0.400) Cancer (0.200)	pINCY
91	384-428 2016-2060	Reproductive (0.221) Gastrointestinal (0.156) Hematopoietic/Immune (0.143)	Cancer (0.468) Inflammation/Trauma (0.325) Cell Proliferation (0.273)	PBLUESCRIPT
92	80-124 731-775	Reproductive (0.286) Hematopoietic/Immune (0.143) Nervous (0.143)	Cancer (0.469) Inflammation/Trauma (0.326) Cell Proliferation (0.306)	PBLUESCRIPT
93	437-481 641-685	Reproductive (0.250) Nervous (0.200) Cardiovascular (0.183)	Cancer (0.550) Inflammation/Trauma (0.284) Cell Proliferation (0.150)	PBLUESCRIPT
94	397-441 1036-1080	Reproductive (0.291) Hematopoietic/Immune (0.228) Nervous (0.152)	Inflammation/Trauma (0.468) Cancer (0.392) Cell Proliferation (0.165)	pINCY
95	247-291	Reproductive (0.242) Hematopoietic/Immune (0.121) Nervous (0.121) Urologic (0.121)	Cancer (0.455) Inflammation/Trauma (0.333) Cell Proliferation (0.273)	pINCY
96	453-497 858-902	Nervous (0.600) Reproductive (0.400)	Cancer (0.400) Inflammation/Trauma (0.200) Neurological (0.200)	pINCY
97	224-268 770-814 1211-1255	Gastrointestinal (0.262) Reproductive (0.215) Nervous (0.169)	Cancer (0.462) Inflammation/Trauma (0.339) Cell Proliferation (0.231)	pINCY
98	3-47 1086-1130	Reproductive (0.211) Gastrointestinal (0.211) Hematopoietic/Immune (0.158)	Cancer (0.553) Cell Proliferation (0.368) Inflammation/Trauma (0.342)	pINCY
99	388-432 874-918	Reproductive (0.268) Nervous (0.146) Cardiovascular (0.146)	Cancer (0.390) Inflammation/Trauma (0.390) Cell Proliferation (0.220)	pINCY
100	26-70	Gastrointestinal (0.238) Cardiovascular (0.190) Hematopoietic/Immune (0.143) Nervous (0.143) Endocrine (0.143)	Cancer (0.429) Inflammation/Trauma (0.381) Cell Proliferation (0.190)	pINCY

Table 3 (cont.)

Nucleotide SEQ ID NO:	Selected Fragments	Tissue Expression (Fraction of Total)	Disease or Condition (Fraction of Total)	Vector
101	226-270 2062-2106	Nervous (0.234) Hematopoietic/Immune (0.170) Reproductive (0.149)	Inflammation/Trauma (0.383) Cancer (0.362) Cell Proliferation (0.213)	pINCY
102	487-531	Reproductive (0.276) Nervous (0.161) Gastrointestinal (0.138) Cardiovascular (0.138)	Cancer (0.494) Cell Proliferation (0.310) Inflammation/Trauma (0.264)	pINCY
103	561-605	Reproductive (0.274) Gastrointestinal (0.194) Cardiovascular (0.129)	Cancer (0.452) Inflammation/Trauma (0.339) Cell Proliferation (0.258)	pINCY
104	287-331 806-850	Gastrointestinal (0.500) Reproductive (0.250) Musculoskeletal (0.250)	Cancer (0.500) Inflammation/Trauma (0.250)	pINCY
105	154-198 505-549 757-801	Gastrointestinal (0.233) Reproductive (0.209) Hematopoietic/Immune (0.163) Nervous (0.163)	Cancer (0.465) Inflammation/Trauma (0.326) Cell Proliferation (0.209)	pINCY
106	174-218 1182-1226	Reproductive (0.185) Hematopoietic/Immune (0.185) Nervous (0.185)	Inflammation/Trauma (0.352) Cell Proliferation (0.333) Cancer (0.315)	pINCY
107	120-164 489-533	Reproductive (0.231) Hematopoietic/Immune (0.231) Nervous (0.154) Cardiovascular (0.154)	Cell Proliferation (0.462) Inflammation/Trauma (0.385) Cancer (0.231)	pINCY
108	64-108 1738-1782	Nervous (0.277) Reproductive (0.255) Cardiovascular (0.160)	Cancer (0.362) Inflammation/Trauma (0.362) Cell Proliferation (0.149)	pINCY
109	415-459 1027-1071 1549-1593	Reproductive (0.274) Hematopoietic/Immune (0.226) Nervous (0.167)	Inflammation/Trauma (0.476) Cancer (0.393) Cell Proliferation (0.179)	pINCY
110	242-286	Reproductive (0.500) Nervous (0.500)	Cancer (1.000)	pINCY
111	488-541 1028-1081	Reproductive (0.270) Nervous (0.191) Gastrointestinal (0.126)	Cancer (0.507) Inflammation/Trauma (0.284) Cell Proliferation (0.172)	PSPORT1



Table 3 (cont.)

Nucleotide SEQ ID NO:	Selected Fragments	Tissue Expression (Fraction of Total)	Disease or Condition (Fraction of Total)	Vector
112	273-326 867-920 1299-1352	Reproductive (0.312) Nervous (0.281) Gastrointestinal (0.094)	Cancer (0.469) Inflammation/Trauma (0.328) Cell Proliferation (0.172)	pINCY
113	866-1135	Reproductive (0.245) Gastrointestinal (0.136) Nervous (0.136)	Cancer (0.445) Cell Proliferation (0.227) Inflammation/Trauma (0.327)	pINCY
114	155-325 812-1105	Nervous (0.314) Reproductive (0.275) Gastrointestinal (0.098)	Cancer (0.471) Inflammation/Trauma (0.118)	pINCY
115	14-298	Gastrointestinal (0.190) Nervous (0.190) Reproductive (0.190)	Cancer (0.476) Cell Proliferation (0.190) Inflammation/Trauma (0.238)	pINCY
116	41-235	Reproductive (0.400) Nervous (0.267) Musculoskeletal (0.133)	Cancer (0.600) Inflammation/Trauma (0.334) Cell Proliferation (0.067)	PSPORT1
117	379-432 973-1026 1297-1350	Reproductive (0.327) Nervous (0.184) Urologic (0.102)	Cancer (0.531) Cell Proliferation (0.224) Inflammation/Trauma (0.265)	pINCY
118	974-1465	Reproductive (0.231) Nervous (0.190) Gastrointestinal (0.169)	Cancer (0.446) Inflammation/Trauma (0.343) Cell Proliferation (0.226)	pINCY
119	543-1028	Reproductive (0.292) Nervous (0.163) Gastrointestinal (0.139)	Cancer (0.517) Cell Proliferation (0.167) Inflammation/Trauma (0.235)	PSPORT1
120	385-552	Nervous (0.571) Cardiovascular (0.143) Developmental (0.143)	Cancer (0.429) Inflammation/Trauma (0.572) Cell Proliferation (0.143)	pINCY
121	685-864	Nervous (0.300) Hematopoietic/Immune (0.200) Cardiovascular (0.140)	Cancer (0.340) Inflammation/Trauma (0.440) Cell Proliferation (0.200)	pINCY
122	703-1026	Reproductive (0.400) Cardiovascular (0.160) Nervous (0.160)	Cancer (0.680) Cell Proliferation (0.120) Inflammation/Trauma (0.160)	pINCY
123	830-1351	Reproductive (0.200) Cardiovascular (0.154) Hematopoietic/Immune (0.154)	Cancer (0.415) Cell Proliferation (0.277) Inflammation/Trauma (0.354)	pINCY

Table 3 (cont.)

Nucleotide SEQ ID NO:	Selected Fragments	Tissue Expression (Fraction of Total)	Disease or Condition (Fraction of Total)	Vector
124	272-325	Cardiovascular (0.250) Gastrointestinal (0.250) Musculoskeletal (0.250)	Inflammation/Trauma (0.750)	pINCY
125	130-972	Reproductive (0.180) Cardiovascular (0.160) Hematopoietic/Immune (0.160)	Cancer (0.440) Inflammation/Trauma (0.340) Cell Proliferation (0.220)	pINCY
126	434-973	Reproductive (0.188) Cardiovascular (0.156) Gastrointestinal (0.156)	Cancer (0.422) Inflammation/Trauma (0.328) Cell Proliferation (0.203)	pINCY
127	489-899	Gastrointestinal (0.333) Reproductive (0.333) Nervous (0.125)	Cancer (0.625) Inflammation/Trauma (0.208) Cell Proliferation (0.042)	pINCY
128	19-1242	Reproductive (0.354) Nervous (0.188) Gastrointestinal (0.146)	Cancer (0.562) Cell Proliferation (0.250) Inflammation/Trauma (0.250)	pINCY
129	217-270 541-594	Reproductive (0.364) Cardiovascular (0.182) Gastrointestinal (0.182)	Cancer (0.636) Inflammation/Trauma (0.364)	pINCY
130	115-864	Gastrointestinal (0.250) Hematopoietic/Immune (0.208) Nervous (0.208)	Cancer (0.500) Inflammation/Trauma (0.292)	pINCY
131	255-308	Reproductive (0.265) Nervous (0.169) Gastrointestinal (0.120)	Cancer (0.482) Cell Proliferation (0.349) Inflammation/Trauma (0.253)	pINCY
132	23-541	Nervous (0.909) Endocrine (0.091)	Cancer (0.636) Cell Proliferation (0.091) Inflammation/Trauma (0.182)	pINCY

Table 4

SEQ ID NO:	Library	Library Comment
67	LATRTUT02	Library was constructed using RNA isolated from a myxoma removed from the left atrium of a 43-year-old Caucasian male during annuloplasty. Pathology indicated atrial myxoma. Patient history included pulmonary insufficiency, acute myocardial infarction, atherosclerotic coronary artery disease, and hyperlipidemia. Family history included benign hypertension, acute myocardial infarction, atherosclerotic coronary artery disease, and type II diabetes.
68	PENITUT01	Library was constructed using RNA isolated from tumor tissue removed from the penis of a 64-year-old Caucasian male during penile amputation. Pathology indicated a fungating invasive grade 4 squamous cell carcinoma involving the inner wall of the foreskin and extending onto the glans penis. Patient history included benign neoplasm of the large bowel, atherosclerotic coronary artery disease, angina pectoris, gout, and obesity. Family history included malignant pharyngeal neoplasm, chronic lymphocytic leukemia, and chronic liver disease.
69	BLADTUT04	Library was constructed using RNA isolated from bladder tumor tissue removed from a 60-year-old Caucasian male during a radical cystectomy, prostatectomy, and vasectomy. Pathology indicated grade 3 transitional cell carcinoma in the left bladder wall. Carcinoma in-situ was identified in the dome and trigone. Family history included type I diabetes, a malignant neoplasm of the stomach, atherosclerotic coronary artery disease, and an acute myocardial infarction.
70	BLADTUT06	Library was constructed using RNA isolated from bladder tumor tissue removed from the posterior bladder wall of a 58-year-old Caucasian male during a radical cystectomy, radical prostatectomy, and gastrectomy. Pathology indicated grade 3 transitional cell carcinoma in the left lateral bladder wall. The remaining bladder showed marked cystitis with scattered microscopic foci of transitional cell carcinoma in situ. Patient history included angina and emphysema. Family history included acute myocardial infarction, atherosclerotic coronary artery disease, and type II diabetes.
71	ADRENOT07	Library was constructed using RNA isolated from adrenal tissue removed from a 61-year-old female during a bilateral adrenalectomy. Patient history included an unspecified disorder of the adrenal glands.
72	BRSTNOT19	Library was constructed using RNA isolated from breast tissue removed from a 67-year-old Caucasian female during a unilateral extended simple mastectomy. Pathology for the associated tumor tissue indicated residual invasive lobular carcinoma. Patient history included depressive disorder, benign large bowel neoplasm, and hemorrhoids. Family history included cerebrovascular and cardiovascular disease and lung cancer.

Table 4 (cont.)

SEQ ID NO.	Library	Library Comment
73	SPLNNOT12	Library was constructed using RNA isolated from spleen tissue removed from a 65-year-old female. Pathology indicated the spleen was negative for metastasis. Pathology for the associated tumor tissue indicated well-differentiated neuroendocrine carcinoma (islet cell tumor), nuclear grade 1, forming a dominant mass in the distal pancreas. Multiple smaller tumor nodules were immediately adjacent to the main mass. The liver showed metastatic grade 1 islet cell tumor, forming multiple nodules. Multiple (4) pericholedochal lymph nodes contained metastatic grade 1 islet cell tumor.
74	MONOTXT02	Library was constructed using RNA isolated from treated monocytes from peripheral blood removed from a 42-year-old female. The cells were treated with interleukin-10 (IL-10) and lipopolysaccharide (LPS). IL-10 was added at time 0 at 10 ng/ml, LPS was added at 1 hour at 5 ng/ml. The monocytes were isolated from buffy coat by adherence to plastic. Incubation time was 24 hours.
75	FIBPFEN06	Library was constructed from 1.56 million independent clones from a prostate stromal fibroblast tissue library. Starting RNA was made from fibroblasts of prostate stroma removed from a male fetus, who died after 26 weeks' gestation. The libraries were normalized in two rounds using conditions adapted from Soares et al. (1994) Proc. Natl. Acad. Sci. USA 91:9228 and Bonaldo et al. (1996) Genome Research 6:791, except that a significantly longer (48-hours/round) reannealing hybridization was used.
76	HUVESTB01	Library was constructed using RNA isolated from shear-stressed HUV-EC-C (ATCC CRL 1730) cells. Before RNA isolation, the cells were subjected to a shear stress of 10 dynes/cm.
77	SYNOCAT01	Library was constructed using RNA isolated from the knee synovial membrane tissue of an 82-year-old female with osteoarthritis.
78	UTRSNOT05	Library was constructed using RNA isolated from the uterine tissue of a 45-year-old Caucasian female during a total abdominal hysterectomy and total colectomy. Pathology for the associated tumor tissue indicated multiple leiomyomas of the myometrium and a grade 2 colonic adenocarcinoma of the cecum. Patient history included multiple sclerosis and mitral valve disorder. Family history included type I diabetes, cerebrovascular disease, atherosclerotic coronary artery disease, malignant skin neoplasm, hypertension, and malignant neoplasm of the colon.
79	HIPONON01	Library was constructed from 1.13 million independent clones from a hippocampus library. RNA was isolated from the hippocampus tissue of a 72-year-old Caucasian female who died from an intracranial bleed. Patient history included nose cancer, hypertension, and arthritis. The normalization and hybridization conditions were adapted from Soares et al. (1994) Proc. Natl. Acad. Sci. USA 91:9228.

Table 4 (cont.)

SEQ ID NO:	Library	Library Comment
80	BRSTTUT03	Library was constructed using RNA isolated from breast tumor tissue removed from a 58-year-old Caucasian female during a unilateral extended simple mastectomy. Pathology indicated multicentric invasive grade 4 lobular carcinoma. The mass was identified in the upper outer quadrant, and three separate nodules were found in the lower outer quadrant of the left breast. Patient history included skin cancer, rheumatic heart disease, osteoarthritis, and tuberculosis. Family history included cerebrovascular disease, coronary artery aneurysm, breast cancer, prostate cancer, atherosclerotic coronary artery disease, and type I diabetes.
81	SININOT01	Library was constructed using RNA isolated from ileum tissue obtained from the small intestine of a 4-year-old Caucasian female, who died from a closed head injury. Patient history included jaundice. Previous surgeries included a double hernia repair.
82	SINTFET03	Library was constructed using RNA isolated from small intestine tissue removed from a Caucasian female fetus, who died at 20 weeks' gestation.
83	HNT3AZT01	Library was constructed using RNA isolated from the hNT2 cell line (derived from a human teratocarcinoma that exhibited properties characteristic of a committed neuronal precursor). Cells were treated for three days with 0.35 micromolar 5-aza-2'-deoxycytidine (AZ).
84	ENDANOT01	Library was constructed using RNA isolated from aortic endothelial cell tissue from an explanted heart removed from a male during a heart transplant.
85	LUNGTUT08	Library was constructed using RNA isolated from lung tumor tissue removed from a 63-year-old Caucasian male during a right upper lobectomy with fiberoptic bronchoscopy. Pathology indicated a grade 3 adenocarcinoma. Patient history included atherosclerotic coronary artery disease, an acute myocardial infarction, rectal cancer, an asymptomatic abdominal aortic aneurysm, tobacco abuse, and cardiac dysrhythmia. Family history included congestive heart failure, stomach cancer, and lung cancer, type II diabetes, atherosclerotic coronary artery disease, and an acute myocardial infarction.
86	OVARTUT10	Library was constructed using RNA isolated from ovarian tumor tissue removed from the left ovary of a 58-year-old Caucasian female during a total abdominal hysterectomy, removal of a solitary ovary, and repair of inguinal hernia. Pathology indicated a metastatic grade 3 adenocarcinoma of colonic origin, forming a partially cystic and necrotic tumor mass in the left ovary, and an adenocarcinoma of colonic origin, forming a nodule in the left mesovarium. A single intramural leiomyoma was identified in the myometrium. The cervix showed mild chronic cystic cervicitis. Patient history included benign hypertension, follicular cyst of the ovary, colon cancer, benign colon neoplasm, and osteoarthritis. Family history included emphysema, myocardial infarction, atherosclerotic coronary artery disease, benign hypertension, and hyperlipidemia.

Table 4 (cont.)

SEQ ID NO:	Library	Library Comment
87	BRSTNOT13	Library was constructed using RNA isolated from breast tissue removed from a 36-year-old Caucasian female during bilateral simple mastectomy. Patient history included a breast neoplasm, depressive disorder, hyperlipidemia, and a chronic stomach ulcer. Family history included cardiovascular and cerebrovascular disease; hyperlipidemia; skin, breast, esophageal, bladder, and bone cancer; and Hodgkin's lymphoma.
88	UTRSNOR01	Library was constructed using RNA isolated from uterine endometrium tissue removed from a 29-year-old Caucasian female during a vaginal hysterectomy and cystocele repair. Pathology indicated the endometrium was secretory, and the cervix showed mild chronic cervicitis with focal squamous metaplasia. Pathology for the associated tumor tissue indicated intramural uterine leiomyoma. Patient history included hypothyroidism, pelvic floor relaxation, and paraplegia. Family history included benign hypertension, type II diabetes, and hyperlipidemia.
89	BRSTTMT02	Library was constructed using RNA isolated from diseased right breast tissue removed from a 46-year-old Caucasian female during a unilateral extended simple mastectomy and open breast biopsy. Pathology indicated mildly proliferative fibrocystic change, including intraductal duct ectasia, papilloma formation, and ductal hyperplasia. Pathology for the associated tumor tissue indicated multifocal ductal carcinoma in situ, both comedo and non-comedo types, nuclear grade 2 with extensive intraductal calcifications. Patient history included deficiency anemia, normal delivery, chronic sinusitis, extrinsic asthma, and kidney infection. Family history included type II diabetes, benign hypertension, cerebrovascular disease, skin cancer, and hyperlipidemia.
90	LIVRDIR01	Library was constructed using RNA isolated from diseased liver tissue removed from a 63-year-old Caucasian female during a liver transplant. Patient history included primary biliary cirrhosis. Serology was positive for anti-mitochondrial antibody.
91	HUVENOB01	Library was constructed using RNA isolated from HUV-EC-C (ATCC CRL 1730) cells.
92	TESTNOT03	Library was constructed using RNA isolated from testicular tissue removed from a 37-year-old Caucasian male, who died from liver disease. Patient history included cirrhosis, jaundice, and liver failure.
93	LUNGNOT02	Library was constructed using RNA isolated from the lung tissue of a 47-year-old Caucasian male, who died of a subarachnoid hemorrhage.
94	LUNGFET03	Library was constructed using RNA isolated from lung tissue removed from a Caucasian female fetus, who died at 20 weeks' gestation.
95	PANCNOT07	Library was constructed using RNA isolated from the pancreatic tissue of a Caucasian male fetus, who died at 23 weeks' gestation.

Table 4 (cont.)

SEQ ID No.	Library	Library Comment
96	BRAINOT12	Library was constructed using RNA isolated from brain tissue removed from the right frontal lobe of a 5-year-old Caucasian male during a hemispherectomy. Pathology indicated extensive polymicrogyria and mild to moderate gliosis (predominantly subpial and subcortical), which are consistent with chronic seizure disorder. Family history included a cervical neoplasm.
97	LIVRTUT01	Library was constructed using RNA isolated from liver tumor tissue removed from a 51-year-old Caucasian female during a hepatic lobectomy. Pathology indicated metastatic grade 3 adenocarcinoma consistent with colon cancer. Family history included a malignant neoplasm of the liver.
98	GBLATUT01	Library was constructed using RNA isolated from gall bladder tumor tissue removed from a 78-year-old Caucasian female during a cholecystectomy. Pathology indicated invasive grade 2 squamous cell carcinoma, forming a mass in the gall bladder. Patient history included diverticulitis of the colon, palpitations, benign hypertension, and hyperlipidemia. Family history included a cholecystectomy, atherosclerotic coronary artery disease, hyperlipidemia, and benign hypertension.
99	LEUKNOT02	Library was constructed using RNA isolated from white blood cells of a 45-year-old female with blood type O+. The donor tested positive for cytomegalovirus (CMV).
100	LUNGNOT22	Library was constructed using RNA isolated from lung tissue removed from a 58-year-old Caucasian female. The tissue sample used to construct this library was found to have tumor contaminant upon microscopic examination. Pathology for the associated tumor tissue indicated a caseating granuloma. Family history included congestive heart failure, breast cancer, secondary bone cancer, acute myocardial infarction and atherosclerotic coronary artery disease.
101	ADRETUT06	Library was constructed using RNA isolated from adrenal tumor tissue removed from a 57-year-old Caucasian female during a unilateral right adrenalectomy. Pathology indicated pheochromocytoma, forming a nodular mass completely replacing the medulla of the adrenal gland.
102	ADRETUT06	Library was constructed using RNA isolated from adrenal tumor tissue removed from a 57-year-old Caucasian female during a unilateral right adrenalectomy. Pathology indicated pheochromocytoma, forming a nodular mass completely replacing the medulla of the adrenal gland.
103	THVRNOT10	Library was constructed using RNA isolated from diseased left thyroid tissue removed from a 30-year-old Caucasian female during a unilateral thyroid lobectomy and parathyroid reimplantation. Pathology indicated lymphocytic thyroiditis.



Table 4 (cont.)

SEQ ID NO:	Library	Library Comment
104	CONNTUT05	Library was constructed using RNA isolated from tumorous skull soft tissue removed from a 34-year-old Caucasian female during skull lesion excision. Pathology indicated grade 3 ependymoma forming an implant in the dermis and subcutis associated with dense fibrosis. Patient history included seizures, bone cancer, and brain cancer. Surgeries included cranioplasty and cerebral meninges lesion excision, and treatment included whole brain radiation. Family history included anxiety and depression.
105	HEANOT01	Library was constructed using RNA isolated from right coronary and right circumflex coronary artery tissue removed from the explanted heart of a 46-year-old Caucasian male during a heart transplantation. Patient history included myocardial infarction from total occlusion of the left anterior descending coronary artery, atherosclerotic coronary artery disease, hyperlipidemia, myocardial ischemia, dilated cardiomyopathy, left ventricular dysfunction, and tobacco abuse. Family history included atherosclerotic coronary artery disease.
106	UTRMTMT01	Library was constructed using RNA isolated from myometrial tissue removed from a 45-year-old Caucasian female during vaginal hysterectomy and bilateral salpingo-oophorectomy. Pathology indicated the myometrium was negative for tumor. Pathology for the associated tumor tissue indicated multiple (23) subserosal, intramural, and submucosal leiomyomata. The endometrium was in proliferative phase. The right ovary contained an old corpus luteum. The cervix, left ovary, and right and left fallopian tubes were unremarkable. The patient presented with stress incontinence. Patient history included extrinsic asthma without status asthmaticus and normal delivery. Patient medications included Motrin, iron sulfate, Premarin, prednisone, Tylenol #3, and Colace. Family history included cerebrovascular disease, depression, and atherosclerotic coronary artery disease.
107	FIBPFEN06	This normalized library was constructed from 1.56 million independent clones from a prostate stromal fibroblast library. RNA was isolated from a male fetus, who died after 26 weeks' gestation. The normalization and hybridization conditions were adapted from Soares et al. (1994) Proc. Natl. Acad. Sci. USA 91:9228.



Table 4 (cont.)

SEQ ID NO.	Library	Library Comment
108	BRAINOT19	Library was constructed using RNA isolated from diseased brain tissue removed from the left frontal lobe of a 27-year-old Caucasian male during a brain lobectomy. Pathology indicated a focal deep white matter lesion, characterized by marked gliosis, calcifications, and hemosiderin-laden macrophages, consistent with a remote perinatal injury. This tissue also showed mild to moderate generalized gliosis, predominantly subpial and subcortical, consistent with chronic seizure disorder. The left temporal lobe, including the mesial temporal structures, showed focal, marked pyramidal cell loss and gliosis in hippocampal sector CA1, consistent with mesial temporal sclerosis. GFAP was positive for astrocytes. Patient presented with intractable epilepsy, focal epilepsy, hemiplegia, and an unspecified brain injury. Patient history included cerebral palsy, abnormality of gait, and depressive disorder. Family history included brain cancer.
109	COLCDIT03	Library was constructed using RNA isolated from diseased colon polyp tissue removed from the cecum of a 67-year-old female. Pathology indicated a benign cecum polyp. Pathology for the associated tumor tissue indicated invasive grade 3 adenocarcinoma that arose in tubulovillous adenoma forming a fungating mass in the cecum.
110	BRAXNOT03	Library was constructed using RNA isolated from sensory-motor cortex tissue removed from the brain of a 35-year-old Caucasian male who died from cardiac failure. Pathology indicated moderate leptomeningeal fibrosis and multiple microinfarctions of the cerebral neocortex. The cerebral hemisphere revealed moderate fibrosis of the leptomeninges with focal calcifications. There was evidence of shrunken and slightly eosinophilic pyramidal neurons throughout the cerebral hemispheres. There were also multiple small microscopic areas of cavitation with surrounding gliosis, scattered throughout the cerebral cortex. Patient history included dilated cardiomyopathy, congestive heart failure, cardiomegaly and an enlarged spleen and liver. Patient medications included Simethicone, Lasix, Digoxin, Colace, Zantac, Captopril, and Vasotec.
111	BRAITUT02	Library was constructed using RNA isolated from brain tumor tissue removed from the frontal lobe of a 58-year-old Caucasian male during excision of a cerebral meningeal lesion. Pathology indicated a grade 2 metastatic hypernephroma. Patient history included a grade 2 renal cell carcinoma, insomnia, and chronic airway obstruction. Family history included a malignant neoplasm of the kidney.
112	PROSNOT11	Library was constructed using RNA isolated from the prostate tissue of a 28-year-old Caucasian male, who died from a self-inflicted gunshot wound.
113	LIVRTUT01	Library was constructed using RNA isolated from liver tumor tissue removed from a 51-year-old Caucasian female during a hepatic lobectomy. Pathology indicated metastatic grade 3 adenocarcinoma consistent with colon cancer. Family history included a malignant neoplasm of the liver.

Table 4 (cont.)

SEQ ID NO.	Library	Library Comment
114	PANCTUT02	Library was constructed using RNA isolated from pancreatic tumor tissue removed from a 45-year-old Caucasian female during radical pancreaticoduodenectomy. Pathology indicated a grade 4 anaplastic carcinoma. Family history included benign hypertension, hyperlipidemia and atherosclerotic coronary artery disease.
115	LIVRFET02	Library was constructed using RNA isolated from liver tissue removed from a Caucasian female fetus, who died at 20 weeks' gestation. Family history included seven days of erythromycin treatment for bronchitis in the mother during the first trimester.
116	BRAITUT03	Library was constructed using RNA isolated from brain tumor tissue removed from the left frontal lobe a 17-year-old Caucasian female during excision of a cerebral meningeal lesion. Pathology indicated a grade 4 fibrillary giant and small-cell astrocytoma. Family history included benign hypertension and cerebrovascular disease.
117	BRSTNOT07	Library was constructed using RNA isolated from diseased breast tissue removed from a 43-year-old Caucasian female during a unilateral extended simple mastectomy. Pathology indicated mildly proliferative fibrocystic changes with epithelial hyperplasia, papillomatosis, and duct ectasia. Pathology for the associated tumor tissue indicated invasive grade 4, nuclear grade 3 mammary adenocarcinoma with extensive comedo necrosis. Family history included epilepsy, cardiovascular disease, and type II diabetes.
118	SMCANOT01	Library was constructed using RNA isolated from an aortic smooth muscle cell line derived from the explanted heart of a male during a heart transplant.
119	THP1AZS08	Library was constructed using 5.76 million clones from a 5-aza-2'-deoxycytidine (AZ) treated THP-1 promonocyte cell line library. Starting RNA was made from THP-1 promonocyte cells treated for three days with 0.8 micromolar AZ. The hybridization probe for subtraction was derived from a similarly constructed library, made from 1 microgram of polyA RNA isolated from untreated THP-1 cells. 5.76 million clones from the AZ-treated THP-1 cell library were then subjected to two rounds of subtractive hybridization with 5 million clones from the untreated THP-1 cell library. Subtractive hybridization conditions were based on the methodologies of Swaroop et al. (1991) Nucleic Acids Res. 19:1954, and Bonaldo et al. (1996) Genome Research 6:791. THP-1 (ATCC TIB 202) is a human promonocyte line derived from peripheral blood of a 1-year-old Caucasian male with acute monocytic leukemia (ref: Int. J. Cancer (1980) 26:171).
120	ADRETUT06	Library was constructed using RNA isolated from adrenal tumor tissue removed from a 57-year-old Caucasian female during a unilateral right adrenalectomy. Pathology indicated pheochromocytoma, forming a nodular mass completely replacing the medulla of the adrenal gland.

Table 4 (cont.)

SEQ ID NO:	Library	Library Comment
121	SININOT03	Library was constructed using RNA isolated from ileum tissue obtained from an 8-year-old Caucasian female, who died from head trauma. Serology was positive for cytomegalovirus (CMV).
122	SININOT03	Library was constructed using RNA isolated from ileum tissue obtained from an 8-year-old Caucasian female, who died from head trauma. Serology was positive for cytomegalovirus (CMV).
123	TYMNOT06	Library was constructed using RNA isolated from activated Th2 cells. These cells were differentiated from umbilical cord CD4 T cells with IL-4 in the presence of anti-IL-12 antibodies and B7-transfected COS cells, and then activated for six hours with anti-CD3 and anti-CD28 antibodies.
124	HEAANOT01	Library was constructed using RNA isolated from right coronary and right circumflex coronary artery tissue removed from the explanted heart of a 46-year-old Caucasian male during a heart transplantation. Patient history included myocardial infarction from total occlusion of the left anterior descending coronary artery, atherosclerotic coronary artery disease, hyperlipidemia, myocardial ischemia, dilated cardiomyopathy, left ventricular dysfunction, and tobacco abuse. Previous surgeries included cardiac catheterization. Family history included atherosclerotic coronary artery disease.
125	TLVJINT01	Library was constructed using RNA isolated from a Jurkat cell line derived from the T cells of a male. The cells were treated for 18 hours with 50 ng/ml phorbol ester (PMA) and 1 micromolar calcium ionophore. Patient history included acute T-cell leukemia.
126	BRAITUT24	Library was constructed using RNA isolated from right frontal brain tumor tissue removed from a 50-year-old Caucasian male during a cerebral meninges lesion excision. Pathology indicated meningioma. Family history included colon cancer and cerebrovascular disease.
127	PROSTUT16	Library was constructed using RNA isolated from prostate tumor tissue removed from a 55-year-old Caucasian male. Pathology indicated adenocarcinoma, Gleason grade 5+4. Adenofibromatous hyperplasia was also present. The patient presented with elevated prostate specific antigen (PSA). Patient history included calculus of the kidney. Family history included lung cancer and breast cancer.
128	BRONNOT01	Library was constructed using RNA isolated from bronchial tissue removed from a 15-year-old Caucasian male.

Table 4 (cont.)

SEQ ID NO:	Library	Library Comment
129	BLADTUT03	Library was constructed using RNA isolated from bladder tumor tissue removed from a 58-year-old Caucasian male during a radical cystectomy, radical prostatectomy, regional lymph node excision, and urinary diversion to bowel. Pathology indicated invasive grade 3 transitional cell carcinoma. Patient history included a benign colon neoplasm. Family history included cerebrovascular disease and atherosclerotic coronary artery disease.
130	COLXTDT01	Library was constructed using RNA isolated from colon tissue removed from the appendix of a 37-year-old Black female during myomectomy, dilation and curettage, right fimbrial region biopsy, and incidental appendectomy. Pathology indicated an unremarkable appendix. Pathology for the associated tumor tissue indicated multiple (12) uterine leiomyomata. Patient history included premenopausal menorrhagia and sarcoidosis of the lung. Family history included acute myocardial infarction and atherosclerotic coronary artery disease.
131	BRATNOT02	Library was constructed using RNA isolated from superior temporal cortex tissue removed from the brain of a 35-year-old Caucasian male. No neuropathology was found. Patient history included dilated cardiomyopathy, congestive heart failure, and an enlarged spleen and liver.
132	BRAWNOT01	Library was constructed using RNA isolated from dentate nucleus tissue removed from the brain of a 35-year-old Caucasian male who died from cardiac failure. Pathology indicated moderate leptomeningeal fibrosis and multiple microinfarctions of the cerebral neocortex. Patient history included dilated cardiomyopathy, congestive heart failure, cardiomegaly, and an enlarged spleen and liver.

Table 5 (cont.)

Program	Description	Reference	Parameter Threshold
ProfileScan	An algorithm that searches for structural and sequence motifs in protein sequences that match sequence patterns defined in Prosite.	Gribskov, M. et al. (1988) CABIOS 4:61-66; Gribskov, M. et al. (1989) Methods Enzymol. 183:146-159; Bairoch, A. et al. (1997) Nucleic Acids Res. 25:217-221.	Normalized quality score $\geq$ GCG-specified "HIGH" value for that particular Prosite motif. Generally, score=1.4-2.1.
Phred	A base-calling algorithm that examines automated sequencer traces with high sensitivity and probability.	Ewing, B. et al. (1998) Genome Res. 8:175-185; Ewing, B. and P. Green (1998) Genome Res. 8:186-194.	
Phrap	A Phils Revised Assembly Program including SWAT and CrossMatch, programs based on efficient implementation of the Smith-Waterman algorithm, useful in searching sequence homology and assembling DNA sequences.	Smith, T.F. and M.S. Waterman (1981) Adv. Appl. Math. 2:482-489; Smith, T.F. and M.S. Waterman (1981) J. Mol. Biol. 147:195-197; and Green, P., University of Washington, Seattle, WA.	Score= 120 or greater; Match length= 56 or greater
Consed	A graphical tool for viewing and editing Phrap assemblies.	Gordon, D. et al. (1998) Genome Res. 8:195-202.	
SPScan	A weight matrix analysis program that scans protein sequences for the presence of secretory signal peptides.	Nielson, H. et al. (1997) Protein Engineering 10:1-6; Claverie, J.M. and S. Audic (1997) CABIOS 12:431-439.	Score=3.5 or greater
Motifs	A program that searches amino acid sequences for patterns that matched those defined in Prosite.	Bairoch, A. et al. (1997) Nucleic Acids Res. 25:217-221; Wisconsin Package Program Manual, version 9, page M51-59, Genetics Computer Group, Madison, WI.	

What is claimed is:

1. An isolated polypeptide comprising an amino acid sequence selected from the group consisting of:

5 a) an amino acid sequence selected from the group consisting of SEQ ID NO:1, SEQ ID NO:2, SEQ ID NO:3, SEQ ID NO:4, SEQ ID NO:5, SEQ ID NO:6, SEQ ID NO:7, SEQ ID NO:8, SEQ ID NO:9, SEQ ID NO:10, SEQ ID NO:11, SEQ ID NO:12, SEQ ID NO:13, SEQ ID NO:14, SEQ ID NO:15, SEQ ID NO:16, SEQ ID NO:17, SEQ ID NO:18, SEQ ID NO:19, SEQ ID NO:20, SEQ ID NO:21, SEQ ID NO:22, SEQ ID NO:24, SEQ ID NO:25, SEQ ID NO:26, SEQ ID NO:27,  
10 SEQ ID NO:29, SEQ ID NO:30, SEQ ID NO:31, SEQ ID NO:32, SEQ ID NO:33, SEQ ID NO:34, SEQ ID NO:36, SEQ ID NO:37, SEQ ID NO:38, SEQ ID NO:39, SEQ ID NO:40, SEQ ID NO:41, SEQ ID NO:43, SEQ ID NO:44, SEQ ID NO:45, SEQ ID NO:46, SEQ ID NO:47, SEQ ID NO:48, SEQ ID NO:49, SEQ ID NO:50, SEQ ID NO:52, SEQ ID NO:53, SEQ ID NO:54, SEQ ID NO:55, SEQ ID NO:56, SEQ ID NO:57, SEQ ID NO:58, SEQ ID NO:59, SEQ ID NO:60, SEQ ID NO:61,  
15 SEQ ID NO:62, SEQ ID NO:63, SEQ ID NO:64, SEQ ID NO:65, and SEQ ID NO:66,

b) a naturally occurring amino acid sequence having at least 90% sequence identity to an amino acid sequence selected from the group consisting of SEQ ID NO:1, SEQ ID NO:2, SEQ ID NO:3, SEQ ID NO:4, SEQ ID NO:5, SEQ ID NO:6, SEQ ID NO:7, SEQ ID NO:8, SEQ ID NO:9, SEQ ID NO:10, SEQ ID NO:11, SEQ ID NO:12, SEQ ID NO:13, SEQ ID NO:14, SEQ ID NO:15,  
20 SEQ ID NO:16, SEQ ID NO:17, SEQ ID NO:18, SEQ ID NO:19, SEQ ID NO:20, SEQ ID NO:21, SEQ ID NO:22, SEQ ID NO:24, SEQ ID NO:25, SEQ ID NO:26, SEQ ID NO:27, SEQ ID NO:29, SEQ ID NO:30, SEQ ID NO:31, SEQ ID NO:32, SEQ ID NO:33, SEQ ID NO:34, SEQ ID NO:36, SEQ ID NO:37, SEQ ID NO:38, SEQ ID NO:39, SEQ ID NO:40, SEQ ID NO:41, SEQ ID NO:43, SEQ ID NO:44, SEQ ID NO:45, SEQ ID NO:46, SEQ ID NO:47, SEQ ID NO:48, SEQ ID NO:49,  
25 SEQ ID NO:50, SEQ ID NO:52, SEQ ID NO:53, SEQ ID NO:54, SEQ ID NO:55, SEQ ID NO:56, SEQ ID NO:57, SEQ ID NO:58, SEQ ID NO:59, SEQ ID NO:60, SEQ ID NO:61, SEQ ID NO:62, SEQ ID NO:63, SEQ ID NO:64, SEQ ID NO:65, and SEQ ID NO:66,

c) a biologically active fragment of an amino acid sequence selected from the group consisting of SEQ ID NO:1, SEQ ID NO:2, SEQ ID NO:3, SEQ ID NO:4, SEQ ID NO:5, SEQ ID  
30 NO:6, SEQ ID NO:7, SEQ ID NO:8, SEQ ID NO:9, SEQ ID NO:10, SEQ ID NO:11, SEQ ID NO:12, SEQ ID NO:13, SEQ ID NO:14, SEQ ID NO:15, SEQ ID NO:16, SEQ ID NO:17, SEQ ID NO:18, SEQ ID NO:19, SEQ ID NO:20, SEQ ID NO:21, SEQ ID NO:22, SEQ ID NO:24, SEQ ID NO:25, SEQ ID NO:26, SEQ ID NO:27, SEQ ID NO:29, SEQ ID NO:30, SEQ ID NO:31, SEQ ID NO:32, SEQ ID NO:33, SEQ ID NO:34, SEQ ID NO:36, SEQ ID NO:37, SEQ ID NO:38, SEQ ID  
35 NO:39, SEQ ID NO:40, SEQ ID NO:41, SEQ ID NO:43, SEQ ID NO:44, SEQ ID NO:45, SEQ ID NO:46, SEQ ID NO:47, SEQ ID NO:48, SEQ ID NO:49, SEQ ID NO:50, SEQ ID NO:52, SEQ ID

NO:53, SEQ ID NO:54, SEQ ID NO:55, SEQ ID NO:56, SEQ ID NO:57, SEQ ID NO:58, SEQ ID NO:59, SEQ ID NO:60, SEQ ID NO:61, SEQ ID NO:62, SEQ ID NO:63, SEQ ID NO:64, SEQ ID NO:65, and SEQ ID NO:66, and

d) an immunogenic fragment of an amino acid sequence selected from the group consisting of SEQ ID NO:1, SEQ ID NO:2, SEQ ID NO:3, SEQ ID NO:4, SEQ ID NO:5, SEQ ID NO:6, SEQ ID NO:7, SEQ ID NO:8, SEQ ID NO:9, SEQ ID NO:10, SEQ ID NO:11, SEQ ID NO:12, SEQ ID NO:13, SEQ ID NO:14, SEQ ID NO:15, SEQ ID NO:16, SEQ ID NO:17, SEQ ID NO:18, SEQ ID NO:19, SEQ ID NO:20, SEQ ID NO:21, SEQ ID NO:22, SEQ ID NO:24, SEQ ID NO:25, SEQ ID NO:26, SEQ ID NO:27, SEQ ID NO:29, SEQ ID NO:30, SEQ ID NO:31, SEQ ID NO:32, SEQ ID NO:33, SEQ ID NO:34, SEQ ID NO:36, SEQ ID NO:37, SEQ ID NO:38, SEQ ID NO:39, SEQ ID NO:40, SEQ ID NO:41, SEQ ID NO:43, SEQ ID NO:44, SEQ ID NO:45, SEQ ID NO:46, SEQ ID NO:47, SEQ ID NO:48, SEQ ID NO:49, SEQ ID NO:50, SEQ ID NO:52, SEQ ID NO:53, SEQ ID NO:54, SEQ ID NO:55, SEQ ID NO:56, SEQ ID NO:57, SEQ ID NO:58, SEQ ID NO:59, SEQ ID NO:60, SEQ ID NO:61, SEQ ID NO:62, SEQ ID NO:63, SEQ ID NO:64, SEQ ID NO:65, and SEQ ID NO:66.

2. An isolated polypeptide of claim 1 selected from the group consisting of SEQ ID NO:1, SEQ ID NO:2, SEQ ID NO:3, SEQ ID NO:4, SEQ ID NO:5, SEQ ID NO:6, SEQ ID NO:7, SEQ ID NO:8, SEQ ID NO:9, SEQ ID NO:10, SEQ ID NO:11, SEQ ID NO:12, SEQ ID NO:13, SEQ ID NO:14, SEQ ID NO:15, SEQ ID NO:16, SEQ ID NO:17, SEQ ID NO:18, SEQ ID NO:19, SEQ ID NO:20, SEQ ID NO:21, SEQ ID NO:22, SEQ ID NO:24, SEQ ID NO:25, SEQ ID NO:26, SEQ ID NO:27, SEQ ID NO:29, SEQ ID NO:30, SEQ ID NO:31, SEQ ID NO:32, SEQ ID NO:33, SEQ ID NO:34, SEQ ID NO:36, SEQ ID NO:37, SEQ ID NO:38, SEQ ID NO:39, SEQ ID NO:40, SEQ ID NO:41, SEQ ID NO:43, SEQ ID NO:44, SEQ ID NO:45, SEQ ID NO:46, SEQ ID NO:47, SEQ ID NO:48, SEQ ID NO:49, SEQ ID NO:50, SEQ ID NO:52, SEQ ID NO:53, SEQ ID NO:54, SEQ ID NO:55, SEQ ID NO:56, SEQ ID NO:57, SEQ ID NO:58, SEQ ID NO:59, SEQ ID NO:60, SEQ ID NO:61, SEQ ID NO:62, SEQ ID NO:63, SEQ ID NO:64, SEQ ID NO:65, and SEQ ID NO:66.

3. An isolated polynucleotide encoding a polypeptide of claim 1.

4. An isolated polynucleotide encoding a polypeptide of claim 2.

5. An isolated polynucleotide of claim 4 selected from the group consisting of SEQ ID NO:67, SEQ ID NO:68, SEQ ID NO:69, SEQ ID NO:70, SEQ ID NO:71, SEQ ID NO:72, SEQ ID NO:73, SEQ ID NO:74, SEQ ID NO:75, SEQ ID NO:76, SEQ ID NO:77, SEQ ID NO:78, SEQ ID NO:79, SEQ ID NO:80, SEQ ID NO:81, SEQ ID NO:82, SEQ ID NO:83, SEQ ID NO:84, SEQ ID

NO:85, SEQ ID NO:86, SEQ ID NO:87, SEQ ID NO:88, SEQ ID NO:90, SEQ ID NO:91, SEQ ID NO:92, SEQ ID NO:93, SEQ ID NO:95, SEQ ID NO:96, SEQ ID NO:97, SEQ ID NO:98, SEQ ID NO:99, SEQ ID NO:100, SEQ ID NO:102, SEQ ID NO:103, SEQ ID NO:104, SEQ ID NO:105, SEQ ID NO:106, SEQ ID NO:107, SEQ ID NO:109, SEQ ID NO:110, SEQ ID NO:111, SEQ ID  
5 NO:112, SEQ ID NO:113, SEQ ID NO:114, SEQ ID NO:115, SEQ ID NO:116, SEQ ID NO:118, SEQ ID NO:119, SEQ ID NO:120, SEQ ID NO:121, SEQ ID NO:122, SEQ ID NO:123, SEQ ID NO:124, SEQ ID NO:125, SEQ ID NO:126, SEQ ID NO:127, SEQ ID NO:128, SEQ ID NO:129, SEQ ID NO:130, SEQ ID NO:131, and SEQ ID NO:132.

10 6. A recombinant polynucleotide comprising a promoter sequence operably linked to a polynucleotide of claim 3.

7. A cell transformed with a recombinant polynucleotide of claim 6.

15 8. A transgenic organism comprising a recombinant polynucleotide of claim 6.

9. A method for producing a polypeptide of claim 1, the method comprising:

a) culturing a cell under conditions suitable for expression of the polypeptide, wherein said cell is transformed with a recombinant polynucleotide, and said recombinant polynucleotide  
20 comprises a promoter sequence operably linked to a polynucleotide encoding the polypeptide of claim 1, and

b) recovering the polypeptide so expressed.

10. An isolated antibody which specifically binds to a polypeptide of claim 1.

25

11. An isolated polynucleotide comprising a polynucleotide sequence selected from the group consisting of:

a) a polynucleotide sequence selected from the group consisting of SEQ ID NO:67, SEQ ID NO:68, SEQ ID NO:69, SEQ ID NO:70, SEQ ID NO:71, SEQ ID NO:72, SEQ ID NO:73, SEQ ID NO:74, SEQ ID NO:75, SEQ ID NO:76, SEQ ID NO:77, SEQ ID NO:78, SEQ ID NO:79, SEQ ID NO:80, SEQ ID NO:81, SEQ ID NO:82, SEQ ID NO:83, SEQ ID NO:84, SEQ ID NO:85, SEQ ID NO:86, SEQ ID NO:87, SEQ ID NO:88, SEQ ID NO:90, SEQ ID NO:91, SEQ ID NO:92, SEQ ID NO:93, SEQ ID NO:95, SEQ ID NO:96, SEQ ID NO:97, SEQ ID NO:98, SEQ ID NO:99, SEQ ID NO:100, SEQ ID NO:102, SEQ ID NO:103, SEQ ID NO:104, SEQ ID NO:105, SEQ ID NO:106,  
35 SEQ ID NO:107, SEQ ID NO:109, SEQ ID NO:110, SEQ ID NO:111, SEQ ID NO:112, SEQ ID NO:113, SEQ ID NO:114, SEQ ID NO:115, SEQ ID NO:116, SEQ ID NO:118, SEQ ID NO:119,



SEQ ID NO:120, SEQ ID NO:121, SEQ ID NO:122, SEQ ID NO:123, SEQ ID NO:124, SEQ ID NO:125, SEQ ID NO:126, SEQ ID NO:127, SEQ ID NO:128, SEQ ID NO:129, SEQ ID NO:130, SEQ ID NO:131, and SEQ ID NO:132,

b) a naturally occurring polynucleotide sequence having at least 70% sequence identity to a  
5 polynucleotide sequence selected from the group consisting of SEQ ID NO:67, SEQ ID NO:68, SEQ ID NO:69, SEQ ID NO:70, SEQ ID NO:71, SEQ ID NO:72, SEQ ID NO:73, SEQ ID NO:74, SEQ ID NO:75, SEQ ID NO:76, SEQ ID NO:77, SEQ ID NO:78, SEQ ID NO:79, SEQ ID NO:80, SEQ ID NO:81, SEQ ID NO:82, SEQ ID NO:83, SEQ ID NO:84, SEQ ID NO:85, SEQ ID NO:86, SEQ ID NO:87, SEQ ID NO:88, SEQ ID NO:90, SEQ ID NO:91, SEQ ID NO:92, SEQ ID NO:93, SEQ  
10 ID NO:95, SEQ ID NO:96, SEQ ID NO:97, SEQ ID NO:98, SEQ ID NO:99, SEQ ID NO:100, SEQ ID NO:102, SEQ ID NO:103, SEQ ID NO:104, SEQ ID NO:105, SEQ ID NO:106, SEQ ID NO:107, SEQ ID NO:109, SEQ ID NO:110, SEQ ID NO:111, SEQ ID NO:112, SEQ ID NO:113, SEQ ID NO:114, SEQ ID NO:115, SEQ ID NO:116, SEQ ID NO:118, SEQ ID NO:119, SEQ ID NO:120, SEQ ID NO:121, SEQ ID NO:122, SEQ ID NO:123, SEQ ID NO:124, SEQ ID NO:125, SEQ ID  
15 NO:126, SEQ ID NO:127, SEQ ID NO:128, SEQ ID NO:129, SEQ ID NO:130, SEQ ID NO:131, and SEQ ID NO:132,

c) a polynucleotide sequence complementary to a),

d) a polynucleotide sequence complementary to b), and

e) an RNA equivalent of a)-d).

20

12. An isolated polynucleotide comprising at least 60 contiguous nucleotides of a polynucleotide of claim 11.

13. A method for detecting a target polynucleotide in a sample, said target polynucleotide  
25 having a sequence of a polynucleotide of claim 11, the method comprising:

a) hybridizing the sample with a probe comprising at least 20 contiguous nucleotides comprising a sequence complementary to said target polynucleotide in the sample, and which probe specifically hybridizes to said target polynucleotide, under conditions whereby a hybridization complex is formed between said probe and said target polynucleotide or fragments thereof, and

30 b) detecting the presence or absence of said hybridization complex, and, optionally, if present, the amount thereof.

14. A method of claim 13, wherein the probe comprises at least 60 contiguous nucleotides.

35 15. A method for detecting a target polynucleotide in a sample, said target polynucleotide having a sequence of a polynucleotide of claim 11, the method comprising:

a) amplifying said target polynucleotide or fragment thereof using polymerase chain reaction amplification, and

b) detecting the presence or absence of said amplified target polynucleotide or fragment thereof, and, optionally, if present, the amount thereof.

5

16. A composition comprising an effective amount of a polypeptide of claim 1 and a pharmaceutically acceptable excipient.

17. A composition of claim 16, wherein the polypeptide comprises an amino acid sequence  
10 selected from the group consisting of SEQ ID NO:67, SEQ ID NO:68, SEQ ID NO:69, SEQ ID  
NO:70, SEQ ID NO:71, SEQ ID NO:72, SEQ ID NO:73, SEQ ID NO:74, SEQ ID NO:75, SEQ ID  
NO:76, SEQ ID NO:77, SEQ ID NO:78, SEQ ID NO:79, SEQ ID NO:80, SEQ ID NO:81, SEQ ID  
NO:82, SEQ ID NO:83, SEQ ID NO:84, SEQ ID NO:85, SEQ ID NO:86, SEQ ID NO:87, SEQ ID  
NO:88, SEQ ID NO:90, SEQ ID NO:91, SEQ ID NO:92, SEQ ID NO:93, SEQ ID NO:95, SEQ ID  
15 NO:96, SEQ ID NO:97, SEQ ID NO:98, SEQ ID NO:99, SEQ ID NO:100, SEQ ID NO:102, SEQ ID  
NO:103, SEQ ID NO:104, SEQ ID NO:105, SEQ ID NO:106, SEQ ID NO:107, SEQ ID NO:109,  
SEQ ID NO:110, SEQ ID NO:111, SEQ ID NO:112, SEQ ID NO:113, SEQ ID NO:114, SEQ ID  
NO:115, SEQ ID NO:116, SEQ ID NO:118, SEQ ID NO:119, SEQ ID NO:120, SEQ ID NO:121,  
SEQ ID NO:122, SEQ ID NO:123, SEQ ID NO:124, SEQ ID NO:125, SEQ ID NO:126, SEQ ID  
20 NO:127, SEQ ID NO:128, SEQ ID NO:129, SEQ ID NO:130, SEQ ID NO:131, and SEQ ID  
NO:132.

18. A method for treating a disease or condition associated with decreased expression of  
functional GBAP, comprising administering to a patient in need of such treatment the pharmaceutical  
25 composition of claim 16.

19. A method for screening a compound for effectiveness as an agonist of a polypeptide of  
claim 1, the method comprising:

a) exposing a sample comprising a polypeptide of claim 1 to a compound, and  
30 b) detecting agonist activity in the sample.

20. A composition comprising an agonist compound identified by a method of claim 19 and  
a pharmaceutically acceptable excipient.

21. A method for treating a disease or condition associated with decreased expression of  
functional GBAP, comprising administering to a patient in need of such treatment a pharmaceutical

composition of claim 20.

22. A method for screening a compound for effectiveness as an antagonist of a polypeptide of claim 1, the method comprising:

- 5       a) exposing a sample comprising a polypeptide of claim 1 to a compound, and  
      b) detecting antagonist activity in the sample.

23. A composition comprising an antagonist compound identified by a method of claim 22 and a pharmaceutically acceptable excipient.

10

24. A method for treating a disease or condition associated with overexpression of functional GBAP, comprising administering to a patient in need of such treatment a pharmaceutical composition of claim 23.

15

25. A method of screening for a compound that specifically binds to the polypeptide of claim 1, said method comprising the steps of:

- a) combining the polypeptide of claim 1 with at least one test compound under suitable conditions, and  
      b) detecting binding of the polypeptide of claim 1 to the test compound, thereby identifying a  
20   compound that specifically binds to the polypeptide of claim 1.

26. A method of screening for a compound that modulates the activity of the polypeptide of claim 1, said method comprising:

- a) combining the polypeptide of claim 1 with at least one test compound under conditions  
25   permissive for the activity of the polypeptide of claim 1,  
      b) assessing the activity of the polypeptide of claim 1 in the presence of the test compound,  
      and  
      c) comparing the activity of the polypeptide of claim 1 in the presence of the test compound  
      with the activity of the polypeptide of claim 1 in the absence of the test compound, wherein a change  
30   in the activity of the polypeptide of claim 1 in the presence of the test compound is indicative of a  
      compound that modulates the activity of the polypeptide of claim 1.

27. A method for screening a compound for effectiveness in altering expression of a target polynucleotide, wherein said target polynucleotide comprises a sequence of claim 5, the method  
35   comprising:

- a) exposing a sample comprising the target polynucleotide to a compound, and

b) detecting altered expression of the target polynucleotide.

28. A method for assessing toxicity of a test compound, said method comprising:

- a) treating a biological sample containing nucleic acids with the test compound;
- 5       b) hybridizing the nucleic acids of the treated biological sample with a probe comprising at least 20 contiguous nucleotides of a polynucleotide of claim 11 under conditions whereby a specific hybridization complex is formed between said probe and a target polynucleotide in the biological sample, said target polynucleotide comprising a polynucleotide sequence of a polynucleotide of claim 11 or fragment thereof;
- 10       c) quantifying the amount of hybridization complex; and
- d) comparing the amount of hybridization complex in the treated biological sample with the amount of hybridization complex in an untreated biological sample, wherein a difference in the amount of hybridization complex in the treated biological sample is indicative of toxicity of the test compound.

## SEQUENCE LISTING

&lt;110&gt; INCYTE GENOMICS, INC.

YUE, Henry  
 TANG, Y. Tom  
 BANDMAN, Olga  
 HILLMAN, Jennifer L.  
 LAL, Preeti  
 AU-YOUNG, Janice  
 REDDY, Roopa  
 YANG, Junming  
 BAUGHN, Mariah R.  
 LU, Dyung Aina M.  
 AZIMZAI, Yalda  
 PATTERSON, Chandra

&lt;120&gt; GTP-BINDING ASSOCIATED PROTEINS

&lt;130&gt; PF-0714 PCT

&lt;140&gt; To Be Assigned

&lt;141&gt; Herewith

&lt;150&gt; 60/144,595; 60/150,460; 60/159,849

&lt;151&gt; 1999-07-19; 1999-08-23; 1999-10-15

&lt;160&gt; 132

&lt;170&gt; PERL Program

&lt;210&gt; 1

&lt;211&gt; 269

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; misc\_feature

&lt;223&gt; Incyte ID No: 1405545CD1

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Tyr	Gly	Arg	Gln	Asp	Leu	His	Leu	Arg	Ile	Phe	Asp	Pro	Ser	Pro
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Glu	Asp	Ile	Ala	Arg	Ala	Asp	Asn	Ile	Phe	Thr	Ala	Thr	Glu	Arg
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Asn	Arg	Ile	Asp	Tyr	Val	Ser	Ser	Ala	Val	Arg	Ile	Asp	His	Ala
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Pro	Asp	Leu	Pro	Arg	Pro	Glu	Val	Cys	Phe	Ile	Gly	Arg	Ser	Asn
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Val	Gly	Lys	Ser	Ser	Leu	Ile	Lys	Ala	Leu	Phe	Ser	Leu	Ala	Pro
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Glu	Val	Glu	Val	Arg	Val	Ser	Lys	Lys	Pro	Gly	His	Thr	Lys	Lys
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Pro	Gly	Tyr	Gly	Phe	Arg	Ala	Pro	Glu	Asp	Phe	Val	Asp	Met	Val
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Glu	Thr	Tyr	Leu	Lys	Glu	Arg	Arg	Asn	Leu	Lys	Arg	Thr	Phe	Leu

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Leu Val Asp Ser	Val Val Gly Ile Gln	Lys Thr Asp Asn Ile	Ala		
	185		190		195
Ile Glu Met Cys	Glu Glu Phe Ala Leu	Pro Tyr Val Ile Val	Leu		
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Thr Lys Ile Asp	Lys Ser Ser Lys Gly	His Leu Leu Lys Gln	Val		
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Leu Gln Ile Gln	Lys Phe Val Asn Met	Lys Thr Gln Gly Cys	Phe		
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Pro Gln Leu Phe	Pro Val Ser Ala Val	Thr Phe Ser Gly Ile	His		
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&lt;211&gt; 428

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; misc\_feature

&lt;223&gt; Incyte ID No: 1451265CD1

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Trp Glu Leu Gln Arg	Lys Asp Gln Leu	Gln Gln Lys Ile Met	Cys
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Pro Gly Pro Val Thr	Cys Leu Thr Ala	Ser Pro Asn Gly Leu	Tyr
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Gly Lys Asp Cys Leu	Val Leu Val Trp	Ser Leu Cys Ser Val	Leu
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His His Thr Leu Pro	Ile Thr Asp Leu	His Cys Gly Phe Gly	Gly
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Pro Leu Ala Arg Val	Ala Thr Ser Ser	Leu Asp Gln Thr Val	Lys
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Asp Glu Thr Val Arg	Leu Trp Asp Val	Gln Ser Lys Gln Cys	Ile
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&lt;211&gt; 562

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; misc\_feature

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&lt;400&gt; 3

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Thr	Arg	Ala	Pro	Pro	Pro	Ser	Ser	Glu	Ser	Arg	Pro	Pro	Cys	His	
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Gly	Gly	Arg	Gln	Arg	Leu	Ser	Asp	Met	Ser	Ile	Ser	Thr	Ser	Ser	
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Gln	Phe	Met	Thr	Gln	Val	Lys	Asn	Tyr	Leu	Ser	Gln	Ser	Ser	Glu	
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Val	Val	Leu	Glu	Lys	Ala	Met	His	Lys	Cys	Ile	Leu	Lys	Pro	Leu	

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Lys Gly His Val	Glu Ala Met Leu Lys	Asp Phe His Met Ala	Asp		
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Gly Ser Trp Lys	Gln Leu Lys Glu Asn	Leu Gln Leu Val Arg	Gln		
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Arg Asn Pro Gln	Glu Leu Gly Val Phe	Ala Pro Thr Pro Asp	Phe		
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Val Asp Val Glu	Lys Ile Lys Val Lys	Phe Met Thr Met Gln	Lys		
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Lys Leu Ile Tyr	Thr Val Met Glu Asn	Asn Ser Gly Arg Met	Tyr		
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Gly Ala Asp Asp	Phe Leu Pro Val Leu	Thr Tyr Val Ile Ala	Gln		
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Cys Asp Met Leu	Glu Leu Asp Thr Glu	Ile Glu Tyr Met Met	Glu		
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Leu Leu Asp Pro	Ser Leu Leu His Gly	Glu Gly Gly Tyr Tyr	Leu		
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Arg Gln Trp His	Lys Arg Arg Thr Thr	Asn Arg Thr Ile Pro	Ser		
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Val Asp Asp Phe	Gln Asn Tyr Leu Arg	Val Ala Phe Gln Glu	Val		
	455		460		465
Asn Ser Gly Cys	Thr Gly Lys Thr Leu	Leu Val Arg Pro Tyr	Ile		
	470		475		480
Thr Thr Glu Asp	Val Cys Gln Ile Cys	Ala Glu Lys Phe Lys	Val		
	485		490		495
Gly Asp Pro Glu	Glu Tyr Ser Leu Phe	Leu Phe Val Asp Glu	Thr		
	500		505		510
Trp Gln Gln Leu	Ala Glu Asp Thr Tyr	Pro Gln Lys Ile Lys	Ala		
	515		520		525
Glu Leu His Ser	Arg Pro Gln Pro His	Ile Phe His Phe Val	Tyr		
	530		535		540
Lys Arg Ile Lys	Asn Asp Pro Tyr Gly	Ile Ile Phe Gln Asn	Gly		
	545		550		555
Glu Glu Asp Leu	Thr Ser				
	560				

&lt;210&gt; 4

&lt;211&gt; 229

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; misc\_feature

&lt;223&gt; Incyte ID No: 1901373CD1

&lt;400&gt; 4

Met Ala Glu Asp Lys	Thr Lys Pro Ser Glu	Leu Asp Gln Gly Lys	
1	5	10	15
Tyr Asp Ala Asp Asp	Asn Val Lys Ile Ile	Cys Leu Gly Asp Ser	
	20	25	30
Ala Val Gly Lys Ser	Lys Leu Met Glu Arg	Phe Leu Met Asp Gly	
	35	40	45
Phe Gln Pro Gln Gln	Leu Ser Thr Tyr Ala	Leu Thr Leu Tyr Lys	
	50	55	60
His Thr Ala Thr Val	Asp Gly Arg Thr Ile	Leu Val Asp Phe Trp	
	65	70	75
Asp Thr Ala Gly Gln	Glu Arg Phe Gln Ser	Met His Ala Ser Tyr	
	80	85	90



Tyr	His	Lys	Ala	His	Ala	Cys	Ile	Met	Val	Phe	Asp	Val	Gln	Arg
				95					100					105
Lys	Val	Thr	Tyr	Arg	Asn	Leu	Ser	Thr	Trp	Tyr	Thr	Glu	Leu	Arg
				110					115					120
Glu	Phe	Arg	Pro	Glu	Ile	Pro	Cys	Ile	Val	Val	Ala	Asn	Lys	Ile
				125					130					135
Asp	Ala	Asp	Ile	Asn	Val	Thr	Gln	Lys	Ser	Phe	Asn	Phe	Ala	Lys
				140					145					150
Lys	Phe	Ser	Leu	Pro	Leu	Tyr	Phe	Val	Ser	Ala	Ala	Asp	Gly	Thr
				155					160					165
Asn	Val	Val	Lys	Leu	Phe	Asn	Asp	Ala	Ile	Arg	Leu	Ala	Val	Ser
				170					175					180
Tyr	Lys	Gln	Asn	Ser	Gln	Asp	Phe	Met	Asp	Glu	Ile	Phe	Gln	Glu
				185					190					195
Leu	Glu	Asn	Phe	Ser	Leu	Glu	Gln	Glu	Glu	Glu	Asp	Val	Pro	Asp
				200					205					210
Gln	Glu	Gln	Ser	Ser	Ser	Ile	Glu	Thr	Pro	Ser	Glu	Glu	Val	Ala
				215					220					225

Ser Pro His Ser

&lt;210&gt; 5

&lt;211&gt; 360

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; misc\_feature

&lt;223&gt; Incyte ID No: 2367767CD1

&lt;400&gt; 5

Met	Phe	Val	Ala	Arg	Ser	Ile	Ala	Ala	Asp	His	Lys	Asp	Leu	Ile
1				5					10					15
His	Asp	Val	Ser	Phe	Asp	Phe	His	Gly	Arg	Arg	Met	Ala	Thr	Cys
				20					25					30
Ser	Ser	Asp	Gln	Ser	Val	Lys	Val	Trp	Asp	Lys	Ser	Glu	Ser	Gly
				35					40					45
Asp	Trp	His	Cys	Thr	Ala	Ser	Trp	Lys	Thr	His	Ser	Gly	Ser	Val
				50					55					60
Trp	Arg	Val	Thr	Trp	Ala	His	Pro	Glu	Phe	Gly	Gln	Val	Leu	Ala
				65					70					75
Ser	Cys	Ser	Phe	Asp	Arg	Thr	Ala	Ala	Val	Trp	Glu	Glu	Ile	Val
				80					85					90
Gly	Glu	Ser	Asn	Asp	Lys	Leu	Arg	Gly	Gln	Ser	His	Trp	Val	Lys
				95					100					105
Arg	Thr	Thr	Leu	Val	Asp	Ser	Arg	Thr	Ser	Val	Thr	Asp	Val	Lys
				110					115					120
Phe	Ala	Pro	Lys	His	Met	Gly	Leu	Met	Leu	Ala	Thr	Cys	Ser	Ala
				125					130					135
Asp	Gly	Ile	Val	Arg	Ile	Tyr	Glu	Ala	Pro	Asp	Val	Met	Asn	Leu
				140					145					150
Ser	Gln	Trp	Ser	Leu	Gln	His	Glu	Ile	Ser	Cys	Lys	Leu	Ser	Cys
				155					160					165
Ser	Cys	Ile	Ser	Trp	Asn	Pro	Ser	Ser	Ser	Arg	Ala	His	Ser	Pro
				170					175					180
Met	Ile	Ala	Val	Gly	Ser	Asp	Asp	Ser	Ser	Pro	Asn	Ala	Met	Ala
				185					190					195
Lys	Val	Gln	Ile	Phe	Glu	Tyr	Asn	Glu	Asn	Thr	Arg	Lys	Tyr	Ala
				200					205					210
Lys	Ala	Glu	Thr	Leu	Met	Thr	Val	Thr	Asp	Pro	Val	His	Asp	Ile
				215					220					225
Ala	Phe	Ala	Pro	Asn	Leu	Gly	Arg	Ser	Phe	His	Ile	Leu	Ala	Ile
				230					235					240
Ala	Thr	Lys	Asp	Val	Arg	Ile	Phe	Thr	Leu	Lys	Pro	Val	Arg	Lys

	245		250		255
Glu Leu Thr Ser	Ser Gly Gly Pro Thr	Lys Phe Glu Ile His	Ile		
	260		265		270
Val Ala Gln Phe	Asp Asn His Asn Ser	Gln Val Trp Arg Val	Ser		
	275		280		285
Trp Asn Ile Thr	Gly Thr Val Leu Ala	Ser Ser Gly Asp Asp	Gly		
	290		295		300
Cys Val Arg Leu	Trp Lys Ala Asn Tyr	Met Asp Asn Trp Lys	Cys		
	305		310		315
Thr Gly Ile Leu	Lys Gly Asn Gly Ser	Pro Val Asn Gly Ser	Ser		
	320		325		330
Gln Gln Gly Thr	Ser Asn Pro Ser Leu	Gly Ser Asn Ile Pro	Ser		
	335		340		345
Leu Gln Asn Ser	Leu Asn Gly Ser Ser	Ala Gly Arg Lys His	Ser		
	350		355		360

&lt;210&gt; 6

&lt;211&gt; 460

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; misc\_feature

&lt;223&gt; Incyte ID No: 3090433CD1

&lt;400&gt; 6

Met Ala Asn Asp	Pro Leu Glu Gly Phe	His Glu Val Asn Leu Ala	
1	5	10	15
Ser Pro Thr Ser	Pro Asp Leu Leu Gly	Val Tyr Glu Ser Gly Thr	
	20	25	30
Gln Glu Gln Thr	Thr Ser Pro Ser Val	Ile Tyr Arg Pro His Pro	
	35	40	45
Ser Ala Leu Ser	Ser Val Pro Ile Gln	Ala Asn Ala Leu Asp Val	
	50	55	60
Ser Glu Leu Pro	Thr Gln Pro Val Tyr	Ser Ser Pro Arg Arg Leu	
	65	70	75
Asn Cys Ala Glu	Ile Ser Ser Ile Ser	Phe His Val Thr Asp Pro	
	80	85	90
Ala Pro Cys Ser	Thr Ser Gly Val Thr	Ala Gly Leu Thr Lys Leu	
	95	100	105
Thr Thr Arg Lys	Asp Asn Tyr Asn Ala	Glu Arg Glu Phe Leu Gln	
	110	115	120
Gly Ala Thr Ile	Thr Glu Ala Cys Asp	Gly Ser Asp Asp Ile Phe	
	125	130	135
Gly Leu Ser Thr	Asp Ser Leu Ser Arg	Leu Arg Ser Pro Ser Val	
	140	145	150
Leu Glu Val Arg	Glu Lys Gly Tyr Glu	Arg Leu Lys Glu Glu Leu	
	155	160	165
Ala Lys Ala Gln	Arg Glu Leu Lys Leu	Lys Asp Glu Glu Cys Glu	
	170	175	180
Arg Leu Ser Lys	Val Arg Asp Gln Leu	Gly Gln Glu Leu Glu Glu	
	185	190	195
Leu Thr Ala Ser	Leu Phe Glu Glu Ala	His Lys Met Val Arg Glu	
	200	205	210
Ala Asn Ile Lys	Gln Ala Thr Ala Glu	Lys Gln Leu Lys Glu Ala	
	215	220	225
Gln Gly Lys Ile	Asp Val Leu Gln Ala	Glu Val Ala Ala Leu Lys	
	230	235	240
Thr Leu Val Leu	Ser Ser Ser Pro Thr	Ser Pro Thr Gln Glu Pro	
	245	250	255
Leu Pro Gly Gly	Lys Thr Pro Phe Lys	Lys Gly His Thr Arg Asn	
	260	265	270
Lys Ser Thr Ser	Ser Ala Met Ser Gly	Ser His Gln Asp Leu Ser	

275	280	285
Val Ile Gln Pro Ile	Val Lys Asp Cys Lys Glu Ala Asp Leu Ser	
290	295	300
Leu Tyr Asn Glu Phe	Arg Leu Trp Lys Asp Glu Pro Thr Met Asp	
305	310	315
Arg Thr Cys Pro Phe	Leu Asp Lys Ile Tyr Gln Glu Asp Ile Phe	
320	325	330
Pro Cys Leu Thr Phe	Ser Lys Ser Glu Leu Ala Ser Ala Val Leu	
335	340	345
Glu Ala Val Glu Asn	Asn Thr Leu Ser Ile Glu Pro Val Gly Leu	
350	355	360
Gln Pro Ile Arg Phe	Val Lys Ala Ser Ala Val Glu Cys Gly Gly	
365	370	375
Pro Lys Lys Cys Ala	Leu Thr Gly Gln Ser Lys Ser Cys Lys His	
380	385	390
Arg Ile Lys Leu Gly	Asp Ser Ser Asn Tyr Tyr Tyr Ile Ser Pro	
395	400	405
Phe Cys Arg Tyr Arg	Ile Thr Ser Val Cys Asn Phe Phe Thr Tyr	
410	415	420
Ile Arg Tyr Ile Gln	Gln Gly Leu Val Lys Gln Gln Asp Val Asp	
425	430	435
Gln Met Phe Trp Glu	Val Met Gln Leu Arg Lys Glu Met Ser Leu	
440	445	450
Ala Lys Leu Gly Tyr	Phe Lys Glu Glu Leu	
455	460	

&lt;210&gt; 7

&lt;211&gt; 239

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; misc\_feature

&lt;223&gt; Incyte ID No: 3800591CD1

&lt;400&gt; 7

Met Gln Asp Pro Asn	Ala Asp Thr Glu Trp Asn Asp Ile Leu Arg	
1	5	10
Lys Lys Gly Ile Leu	Pro Pro Lys Glu Ser Leu Lys Glu Leu Glu	
20	25	30
Glu Glu Ala Glu Glu	Gln Arg Ile Leu Gln Gln Ser Val Val	
35	40	45
Lys Thr Tyr Glu Asp	Met Thr Leu Glu Glu Leu Glu Asp His Glu	
50	55	60
Asp Glu Phe Asn Glu	Glu Asp Glu Arg Ala Ile Glu Met Tyr Arg	
65	70	75
Arg Arg Arg Leu Ala	Glu Trp Lys Ala Thr Lys Leu Lys Asn Lys	
80	85	90
Phe Gly Glu Val Leu	Glu Ile Ser Gly Lys Asp Tyr Val Gln Glu	
95	100	105
Val Thr Lys Ala Gly	Glu Gly Leu Trp Val Ile Leu His Leu Tyr	
110	115	120
Lys Gln Gly Ile Pro	Leu Cys Ala Leu Ile Asn Gln His Leu Ser	
125	130	135
Gly Leu Ala Arg Lys	Phe Pro Asp Val Lys Phe Ile Lys Ala Ile	
140	145	150
Ser Thr Thr Cys Ile	Pro Asn Tyr Pro Asp Arg Asn Leu Pro Thr	
155	160	165
Ile Phe Val Tyr Leu	Glu Gly Asp Ile Lys Ala Gln Phe Ile Gly	
170	175	180
Pro Leu Val Phe Gly	Gly Met Asn Leu Thr Arg Asp Glu Leu Glu	
185	190	195
Trp Lys Leu Ser Glu	Ser Gly Ala Ile Met Thr Asp Leu Glu Glu	
200	205	210

Asn Pro Lys Lys Pro Ile Glu Asp Val Leu Leu Ser Ser Val Arg  
 215 220 225  
 Arg Ser Val Leu Met Lys Arg Asp Ser Asp Ser Glu Gly Asp  
 230 235

<210> 8  
 <211> 334  
 <212> PRT  
 <213> Homo sapiens

<220>  
 <221> misc\_feature  
 <223> Incyte ID No: 5308471CD1

<400> 8  
 Met Arg Leu Thr Pro Arg Ala Leu Cys Ser Ala Ala Gln Ala Ala  
 1 5 10 15  
 Trp Arg Glu Asn Phe Pro Leu Cys Gly Arg Asp Val Ala Arg Trp  
 20 25 30  
 Phe Pro Gly His Met Ala Lys Gly Leu Lys Lys Met Gln Ser Ser  
 35 40 45  
 Leu Lys Leu Val Asp Cys Ile Ile Glu Val His Asp Ala Arg Ile  
 50 55 60  
 Pro Leu Ser Gly Arg Asn Pro Leu Phe Gln Glu Thr Leu Gly Leu  
 65 70 75  
 Lys Pro His Leu Leu Val Leu Asn Lys Met Asp Leu Ala Asp Leu  
 80 85 90  
 Thr Glu Gln Gln Lys Ile Met Gln His Leu Glu Gly Glu Gly Leu  
 95 100 105  
 Lys Asn Val Ile Phe Thr Asn Cys Val Lys Asp Glu Asn Val Lys  
 110 115 120  
 Gln Ile Ile Pro Met Val Thr Glu Leu Ile Gly Arg Ser His Arg  
 125 130 135  
 Tyr His Arg Lys Glu Asn Leu Glu Tyr Cys Ile Met Val Ile Gly  
 140 145 150  
 Val Pro Asn Val Gly Lys Ser Ser Leu Ile Asn Ser Leu Arg Arg  
 155 160 165  
 Gln His Leu Arg Lys Gly Lys Ala Thr Arg Val Gly Gly Glu Pro  
 170 175 180  
 Gly Ile Thr Arg Ala Val Met Ser Lys Ile Gln Val Ser Glu Arg  
 185 190 195  
 Pro Leu Met Phe Leu Leu Asp Thr Pro Gly Val Leu Ala Pro Arg  
 200 205 210  
 Ile Glu Ser Val Glu Thr Gly Leu Lys Leu Ala Leu Cys Gly Thr  
 215 220 225  
 Val Leu Asp His Leu Val Gly Glu Glu Thr Met Ala Asp Tyr Leu  
 230 235 240  
 Leu Tyr Thr Leu Asn Lys His Gln Arg Phe Gly Tyr Val Gln His  
 245 250 255  
 Tyr Gly Leu Gly Ser Ala Cys Asp Asn Val Glu Arg Val Leu Lys  
 260 265 270  
 Ser Val Ala Val Lys Leu Gly Lys Thr Gln Lys Val Lys Val Leu  
 275 280 285  
 Thr Gly Thr Gly Asn Val Asn Val Ile Gln Pro Asn Tyr Pro Ala  
 290 295 300  
 Ala Ala Arg Asp Phe Leu Gln Thr Phe Arg Arg Gly Leu Leu Gly  
 305 310 315  
 Ser Val Met Leu Asp Leu Asp Val Leu Arg Gly His Pro Pro Ala  
 320 325 330  
 Glu Thr Leu Pro

<210> 9  
 <211> 341  
 <212> PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; misc\_feature

&lt;223&gt; Incyte ID No: 5324322CD1

&lt;400&gt; 9

Met	Glu	Arg	Ala	Val	Pro	Leu	Ala	Val	Pro	Leu	Gly	Gln	Thr	Glu	
1				5					10					15	
Val	Phe	Gln	Ala	Leu	Gln	Arg	Leu	His	Met	Thr	Ile	Phe	Ser	Gln	
				20					25					30	
Ser	Val	Ser	Pro	Cys	Gly	Lys	Phe	Leu	Ala	Ala	Gly	Asn	Asn	Tyr	
				35					40					45	
Gly	Gln	Ile	Ala	Ile	Phe	Ser	Leu	Ser	Ser	Ala	Leu	Ser	Ser	Glu	
				50					55					60	
Ala	Lys	Glu	Glu	Ser	Lys	Lys	Pro	Val	Val	Thr	Phe	Gln	Ala	His	
				65					70					75	
Asp	Gly	Pro	Val	Tyr	Ser	Met	Val	Ser	Thr	Asp	Arg	His	Leu	Leu	
				80					85					90	
Ser	Ala	Gly	Asp	Gly	Glu	Val	Lys	Ala	Trp	Leu	Trp	Ala	Glu	Met	
				95					100					105	
Leu	Lys	Lys	Gly	Cys	Lys	Glu	Leu	Trp	Arg	Arg	Gln	Pro	Pro	Tyr	
				110					115					120	
Arg	Thr	Ser	Leu	Glu	Val	Pro	Glu	Ile	Asn	Ala	Leu	Leu	Leu	Val	
				125					130					135	
Pro	Lys	Glu	Asn	Ser	Leu	Ile	Leu	Ala	Gly	Gly	Asp	Cys	Gln	Leu	
				140					145					150	
His	Thr	Met	Asp	Leu	Glu	Thr	Gly	Thr	Phe	Thr	Arg	Val	Leu	Arg	
				155					160					165	
Gly	His	Thr	Asp	Tyr	Ile	His	Cys	Leu	Ala	Leu	Arg	Glu	Arg	Ser	
				170					175					180	
Pro	Glu	Val	Leu	Ser	Gly	Gly	Glu	Asp	Gly	Ala	Val	Arg	Leu	Trp	
				185					190					195	
Asp	Leu	Arg	Thr	Ala	Lys	Glu	Val	Gln	Thr	Ile	Glu	Val	Tyr	Lys	
				200					205					210	
His	Glu	Glu	Cys	Ser	Arg	Pro	His	Asn	Gly	Arg	Trp	Ile	Gly	Cys	
				215					220					225	
Leu	Ala	Thr	Asp	Ser	Asp	Trp	Met	Val	Cys	Gly	Gly	Gly	Pro	Ala	
				230					235					240	
Leu	Thr	Leu	Trp	His	Leu	Arg	Ser	Ser	Thr	Pro	Thr	Thr	Ile	Phe	
				245					250					255	
Pro	Ile	Arg	Ala	Pro	Gln	Lys	His	Val	Thr	Phe	Tyr	Gln	Asp	Leu	
				260					265					270	
Ile	Leu	Ser	Ala	Gly	Gln	Gly	Arg	Cys	Val	Asn	Gln	Trp	Gln	Leu	
				275					280					285	
Ser	Gly	Glu	Leu	Lys	Ala	Gln	Val	Pro	Gly	Ser	Ser	Pro	Gly	Leu	
				290					295					300	
Leu	Ser	Leu	Ser	Leu	Asn	Gln	Gln	Pro	Ala	Ala	Pro	Glu	Cys	Lys	
				305					310					315	
Val	Leu	Thr	Ala	Ala	Gly	Asn	Ser	Cys	Arg	Val	Asp	Val	Phe	Thr	
				320					325					330	
Asn	Leu	Gly	Tyr	Arg	Ala	Phe	Ser	Leu	Ser	Phe					
				335					340						

&lt;210&gt; 10

&lt;211&gt; 513

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; misc\_feature

&lt;223&gt; Incyte ID No: 067184CD1

&lt;400&gt; 10

Met	Ser	Ile	Glu	Ile	Glu	Ser	Ser	Asp	Val	Ile	Arg	Leu	Ile	Met
1				5					10					15
Gln	Tyr	Leu	Lys	Glu	Asn	Ser	Leu	His	Arg	Ala	Leu	Ala	Thr	Leu
				20					25					30
Gln	Glu	Glu	Thr	Thr	Val	Ser	Leu	Asn	Thr	Val	Asp	Ser	Ile	Glu
				35					40					45
Ser	Phe	Val	Ala	Asp	Ile	Asn	Ser	Gly	His	Trp	Asp	Thr	Val	Leu
				50					55					60
Gln	Ala	Ile	Gln	Ser	Leu	Lys	Leu	Pro	Asp	Lys	Thr	Leu	Ile	Asp
				65					70					75
Leu	Tyr	Glu	Gln	Val	Val	Leu	Glu	Leu	Ile	Glu	Leu	Arg	Glu	Leu
				80					85					90
Gly	Ala	Ala	Arg	Ser	Leu	Leu	Arg	Gln	Thr	Asp	Pro	Met	Ile	Met
				95					100					105
Leu	Lys	Gln	Thr	Gln	Pro	Glu	Arg	Tyr	Ile	His	Leu	Glu	Asn	Leu
				110					115					120
Leu	Ala	Arg	Ser	Tyr	Phe	Asp	Pro	Arg	Glu	Ala	Tyr	Pro	Asp	Gly
				125					130					135
Ser	Ser	Lys	Glu	Lys	Arg	Arg	Ala	Ala	Ile	Ala	Gln	Ala	Leu	Ala
				140					145					150
Gly	Glu	Val	Ser	Val	Val	Pro	Pro	Ser	Arg	Leu	Met	Ala	Leu	Leu
				155					160					165
Gly	Gln	Ala	Leu	Lys	Trp	Gln	Gln	His	Gln	Gly	Leu	Leu	Pro	Pro
				170					175					180
Gly	Met	Thr	Ile	Asp	Leu	Phe	Arg	Gly	Lys	Ala	Ala	Val	Lys	Asp
				185					190					195
Val	Glu	Glu	Glu	Lys	Phe	Pro	Thr	Gln	Leu	Ser	Arg	His	Ile	Lys
				200					205					210
Phe	Gly	Gln	Lys	Ser	His	Val	Glu	Cys	Ala	Arg	Phe	Ser	Pro	Asp
				215					220					225
Gly	Gln	Tyr	Leu	Val	Thr	Gly	Ser	Val	Asp	Gly	Phe	Ile	Glu	Val
				230					235					240
Trp	Asn	Phe	Thr	Thr	Gly	Lys	Ile	Arg	Lys	Asp	Leu	Lys	Tyr	Gln
				245					250					255
Ala	Gln	Asp	Asn	Phe	Met	Met	Met	Asp	Asp	Ala	Val	Leu	Cys	Met
				260					265					270
Cys	Phe	Ser	Arg	Asp	Thr	Glu	Met	Leu	Ala	Thr	Gly	Ala	Gln	Asp
				275					280					285
Gly	Lys	Ile	Lys	Val	Trp	Lys	Ile	Gln	Ser	Gly	Gln	Cys	Leu	Arg
				290					295					300
Arg	Phe	Glu	Arg	Ala	His	Ser	Lys	Gly	Val	Thr	Cys	Leu	Ser	Phe
				305					310					315
Ser	Lys	Asp	Ser	Ser	Gln	Ile	Leu	Ser	Ala	Ser	Phe	Asp	Gln	Thr
				320					325					330
Ile	Arg	Ile	His	Gly	Leu	Lys	Ser	Gly	Lys	Thr	Leu	Lys	Glu	Phe
				335					340					345
Arg	Gly	His	Ser	Ser	Phe	Val	Asn	Glu	Ala	Thr	Phe	Thr	Gln	Asp
				350					355					360
Gly	His	Tyr	Ile	Ile	Ser	Ala	Ser	Ser	Asp	Gly	Thr	Val	Lys	Ile
				365					370					375
Trp	Asn	Met	Lys	Thr	Thr	Glu	Cys	Ser	Asn	Thr	Phe	Lys	Ser	Leu
				380					385					390
Gly	Ser	Thr	Ala	Gly	Thr	Asp	Ile	Thr	Val	Asn	Ser	Val	Ile	Leu
				395					400					405
Leu	Pro	Lys	Asn	Pro	Glu	His	Phe	Val	Val	Cys	Asn	Arg	Ser	Asn
				410					415					420
Thr	Val	Val	Ile	Met	Asn	Met	Gln	Gly	Gln	Ile	Val	Arg	Ser	Phe
				425					430					435
Ser	Ser	Gly	Lys	Arg	Glu	Gly	Gly	Asp	Phe	Val	Cys	Cys	Ala	Leu
				440					445					450
Ser	Pro	Arg	Gly	Glu	Trp	Ile	Tyr	Cys	Val	Gly	Glu	Asp	Phe	Val
				455					460					465
Leu	Tyr	Cys	Phe	Ser	Thr	Val	Thr	Gly	Lys	Leu	Glu	Arg	Thr	Leu

	470		475		480
Thr Val His Glu Lys	Asp Val Ile Gly	Ile Ala His His Pro	His		
	485		490		495
Gln Asn Leu Ile Ala	Thr Tyr Ser Glu	Asp Gly Leu Leu Lys	Leu		
	500		505		510

Trp Lys Pro

&lt;210&gt; 11

&lt;211&gt; 186

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; misc\_feature

&lt;223&gt; Incyte ID No: 722896CD1

&lt;400&gt; 11

Met Ile Ala Leu Phe	Asn Lys Leu Leu	Asp Trp Phe Lys Ala	Leu
1	5	10	15
Phe Trp Lys Glu Glu	Met Glu Leu Thr	Leu Val Gly Leu Gln	Tyr
	20	25	30
Ser Gly Lys Thr Thr	Phe Val Asn Val	Ile Ala Ser Gly Gln	Phe
	35	40	45
Asn Glu Asp Met Ile	Pro Thr Val Gly	Phe Asn Met Arg Lys	Ile
	50	55	60
Thr Lys Gly Asn Val	Thr Ile Lys Leu	Trp Asp Ile Gly Gly	Gln
	65	70	75
Pro Arg Phe Arg Ser	Met Trp Glu Arg	Tyr Cys Arg Gly Val	Ser
	80	85	90
Ala Ile Val Tyr Met	Val Asp Ala Ala	Asp Gln Glu Lys Ile	Glu
	95	100	105
Ala Ser Lys Asn Glu	Leu His Asn Leu	Leu Asp Lys Pro Gln	Leu
	110	115	120
Gln Gly Ile Pro Val	Leu Val Leu Gly	Asn Lys Arg Asp Leu	Pro
	125	130	135
Gly Ala Leu Asp Glu	Lys Glu Leu Ile	Glu Lys Met Asn Leu	Ser
	140	145	150
Ala Ile Gln Asp Arg	Glu Ile Cys Cys	Tyr Ser Ile Ser Cys	Lys
	155	160	165
Glu Lys Asp Asn Ile	Asp Ile Thr Leu	Gln Trp Leu Ile Gln	His
	170	175	180
Ser Lys Ser Arg Arg	Ser		
	185		

&lt;210&gt; 12

&lt;211&gt; 204

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; misc\_feature

&lt;223&gt; Incyte ID No: 1571739CD1

&lt;400&gt; 12

Met Asn Asp Val Lys	Leu Ala Val Leu	Gly Gly Glu Gly Thr	Gly
1	5	10	15
Lys Ser Ala Leu Thr	Val Arg Phe Leu	Thr Lys Arg Phe Ile	Gly
	20	25	30
Glu Tyr Ala Ser Asn	Phe Glu Ser Ile	Tyr Lys Lys His Leu	Cys
	35	40	45
Leu Glu Arg Lys Gln	Leu Asn Leu Glu	Ile Tyr Asp Pro Cys	Ser
	50	55	60
Gln Thr Gln Lys Ala	Lys Phe Ser Leu	Thr Ser Glu Leu His	Trp
	65	70	75

Ala Asp Gly Phe Val Ile Val Tyr Asp Ile Ser Asp Arg Ser Ser  
80 85 90  
Phe Ala Phe Ala Lys Ala Leu Ile Tyr Arg Ile Arg Glu Pro Gln  
95 100 105  
Thr Ser His Cys Lys Arg Ala Val Glu Ser Ala Val Phe Leu Val  
110 115 120  
Gly Asn Lys Arg Asp Leu Cys His Val Arg Glu Val Gly Trp Glu  
125 130 135  
Glu Gly Gln Lys Leu Ala Leu Glu Asn Arg Cys Gln Phe Cys Glu  
140 145 150  
Leu Ser Ala Ala Glu Gln Ser Leu Glu Val Glu Met Met Phe Ile  
155 160 165  
Arg Ile Ile Lys Asp Ile Leu Ile Asn Phe Lys Leu Lys Glu Lys  
170 175 180  
Arg Arg Pro Ser Gly Ser Lys Ser Met Ala Lys Leu Ile Asn Asn  
185 190 195  
Val Phe Gly Lys Arg Arg Lys Ser Val  
200

&lt;210&gt; 13

&lt;211&gt; 100

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; misc\_feature

&lt;223&gt; Incyte ID No: 1739479CD1

&lt;400&gt; 13

Met Trp Asp Ser Lys Lys Ile Gly Leu Arg Gln His His Cys Arg  
1 5 10 15  
Lys Cys Gly Lys Ala Val Cys Gly Lys Cys Ser Ser Lys Arg Ser  
20 25 30  
Ser Ile Pro Leu Met Gly Phe Glu Phe Glu Val Arg Val Cys Asp  
35 40 45  
Ser Cys His Glu Ala Ile Thr Asp Glu Glu Arg Ala Pro Thr Ala  
50 55 60  
Thr Phe His Asp Ser Lys His Asn Ile Val His Val His Phe Asp  
65 70 75  
Ala Thr Arg Gly Trp Leu Leu Thr Ser Gly Thr Asp Lys Val Ile  
80 85 90  
Lys Leu Trp Asp Met Thr Pro Val Val Ser  
95 100

&lt;210&gt; 14

&lt;211&gt; 795

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; misc\_feature

&lt;223&gt; Incyte ID No: 1999147CD1

&lt;400&gt; 14

Met Thr Ser Gly Ala Thr Arg Tyr Arg Leu Ser Cys Ser Leu Arg  
1 5 10 15  
Gly His Glu Leu Asp Val Arg Gly Leu Val Cys Cys Ala Tyr Pro  
20 25 30  
Pro Gly Ala Phe Val Ser Val Ser Arg Asp Arg Thr Thr Arg Leu  
35 40 45  
Trp Ala Pro Asp Ser Pro Asn Arg Ser Phe Thr Glu Met His Cys  
50 55 60  
Met Ser Gly His Ser Asn Phe Val Ser Cys Val Cys Ile Ile Pro  
65 70 75  
Ser Ser Asp Ile Tyr Pro His Gly Leu Ile Ala Thr Gly Gly Asn



				80					85					90
Asp	His	Asn	Ile	Cys	Ile	Phe	Ser	Leu	Asp	Ser	Pro	Met	Pro	Leu
				95					100					105
Tyr	Ile	Leu	Lys	Gly	His	Lys	Asn	Thr	Val	Cys	Ser	Leu	Ser	Ser
				110					115					120
Gly	Lys	Phe	Gly	Thr	Leu	Leu	Ser	Gly	Ser	Trp	Asp	Thr	Thr	Ala
				125					130					135
Lys	Val	Trp	Leu	Asn	Asp	Lys	Cys	Met	Met	Thr	Leu	Gln	Gly	His
				140					145					150
Thr	Ala	Ala	Val	Trp	Ala	Val	Lys	Ile	Leu	Pro	Glu	Gln	Gly	Leu
				155					160					165
Met	Leu	Thr	Gly	Ser	Ala	Asp	Lys	Thr	Val	Lys	Leu	Trp	Lys	Ala
				170					175					180
Gly	Arg	Cys	Glu	Arg	Thr	Phe	Ser	Gly	His	Glu	Asp	Cys	Val	Arg
				185					190					195
Gly	Leu	Ala	Ile	Leu	Ser	Glu	Thr	Glu	Phe	Leu	Ser	Cys	Ala	Asn
				200					205					210
Asp	Ala	Ser	Ile	Arg	Arg	Trp	Gln	Ile	Thr	Gly	Glu	Cys	Leu	Glu
				215					220					225
Val	Tyr	Tyr	Gly	His	Thr	Asn	Tyr	Ile	Tyr	Ser	Ile	Ser	Val	Phe
				230					235					240
Pro	Asn	Cys	Arg	Asp	Phe	Val	Thr	Thr	Ala	Glu	Asp	Arg	Ser	Leu
				245					250					255
Arg	Ile	Trp	Lys	His	Gly	Glu	Cys	Ala	Gln	Thr	Ile	Arg	Leu	Pro
				260					265					270
Ala	Gln	Ser	Ile	Trp	Cys	Cys	Cys	Val	Leu	Asp	Asn	Gly	Asp	Ile
				275					280					285
Val	Val	Gly	Ala	Ser	Asp	Gly	Ile	Ile	Arg	Val	Phe	Thr	Glu	Ser
				290					295					300
Glu	Asp	Arg	Thr	Ala	Ser	Ala	Glu	Glu	Ile	Lys	Ala	Phe	Glu	Lys
				305					310					315
Glu	Leu	Ser	His	Ala	Thr	Ile	Asp	Ser	Lys	Thr	Gly	Asp	Leu	Gly
				320					325					330
Asp	Ile	Asn	Ala	Glu	Gln	Leu	Pro	Gly	Arg	Glu	His	Leu	Asn	Glu
				335					340					345
Pro	Gly	Thr	Arg	Glu	Gly	Gln	Thr	Arg	Leu	Ile	Arg	Asp	Gly	Glu
				350					355					360
Lys	Val	Glu	Ala	Tyr	Gln	Trp	Ser	Val	Ser	Glu	Gly	Arg	Trp	Ile
				365					370					375
Lys	Ile	Gly	Asp	Val	Val	Gly	Ser	Ser	Gly	Ala	Asn	Gln	Gln	Thr
				380					385					390
Ser	Gly	Lys	Val	Leu	Tyr	Glu	Gly	Lys	Glu	Phe	Asp	Tyr	Val	Phe
				395					400					405
Ser	Ile	Asp	Val	Asn	Glu	Gly	Gly	Pro	Ser	Tyr	Lys	Leu	Pro	Tyr
				410					415					420
Asn	Thr	Ser	Asp	Asp	Pro	Trp	Leu	Thr	Ala	Tyr	Asn	Phe	Leu	Gln
				425					430					435
Lys	Asn	Asp	Leu	Asn	Pro	Met	Phe	Leu	Asp	Gln	Val	Ala	Lys	Phe
				440					445					450
Ile	Ile	Asp	Asn	Thr	Lys	Gly	Gln	Met	Leu	Gly	Leu	Gly	Asn	Pro
				455					460					465
Ser	Phe	Ser	Asp	Pro	Phe	Thr	Gly	Gly	Gly	Arg	Tyr	Val	Pro	Gly
				470					475					480
Ser	Ser	Gly	Ser	Ser	Asn	Thr	Leu	Pro	Thr	Ala	Asp	Pro	Phe	Thr
				485					490					495
Gly	Ala	Gly	Arg	Tyr	Val	Pro	Gly	Ser	Ala	Ser	Met	Gly	Thr	Thr
				500					505					510
Met	Ala	Gly	Val	Asp	Pro	Phe	Thr	Gly	Asn	Ser	Ala	Tyr	Arg	Ser
				515					520					525
Ala	Ala	Ser	Lys	Thr	Met	Asn	Ile	Tyr	Phe	Pro	Lys	Lys	Glu	Ala
				530					535					540
Val	Thr	Phe	Asp	Gln	Ala	Asn	Pro	Thr	Gln	Ile	Leu	Gly	Lys	Leu
				545					550					555

Lys	Glu	Leu	Asn	Gly	Thr	Ala	Pro	Glu	Glu	Lys	Lys	Leu	Thr	Glu
				560					565					570
Asp	Asp	Leu	Ile	Leu	Leu	Glu	Lys	Ile	Leu	Ser	Leu	Ile	Cys	Asn
				575					580					585
Ser	Ser	Ser	Glu	Lys	Pro	Thr	Val	Gln	Gln	Leu	Gln	Ile	Leu	Trp
				590					595					600
Lys	Ala	Ile	Asn	Cys	Pro	Glu	Asp	Ile	Val	Phe	Pro	Ala	Leu	Asp
				605					610					615
Ile	Leu	Arg	Leu	Ser	Ile	Lys	His	Pro	Ser	Val	Asn	Glu	Asn	Phe
				620					625					630
Cys	Asn	Glu	Lys	Glu	Gly	Ala	Gln	Phe	Ser	Ser	His	Leu	Ile	Asn
				635					640					645
Leu	Leu	Asn	Pro	Lys	Gly	Lys	Pro	Ala	Asn	Gln	Leu	Leu	Ala	Leu
				650					655					660
Arg	Thr	Phe	Cys	Asn	Cys	Phe	Val	Gly	Gln	Ala	Gly	Gln	Lys	Leu
				665					670					675
Met	Met	Ser	Gln	Arg	Glu	Ser	Leu	Met	Ser	His	Ala	Ile	Glu	Leu
				680					685					690
Lys	Ser	Gly	Ser	Asn	Lys	Asn	Ile	His	Ile	Ala	Leu	Ala	Thr	Leu
				695					700					705
Ala	Leu	Asn	Tyr	Ser	Val	Cys	Phe	His	Lys	Asp	His	Asn	Ile	Glu
				710					715					720
Gly	Lys	Ala	Gln	Cys	Leu	Ser	Leu	Ile	Ser	Thr	Ile	Leu	Glu	Val
				725					730					735
Val	Gln	Asp	Leu	Glu	Ala	Thr	Phe	Arg	Leu	Leu	Val	Ala	Leu	Gly
				740					745					750
Thr	Leu	Ile	Ser	Asp	Asp	Ser	Asn	Ala	Val	Gln	Leu	Ala	Lys	Ser
				755					760					765
Leu	Gly	Val	Asp	Ser	Gln	Ile	Lys	Lys	Tyr	Ser	Ser	Val	Ser	Glu
				770					775					780
Pro	Ala	Lys	Val	Ser	Glu	Cys	Cys	Arg	Phe	Ile	Leu	Asn	Leu	Leu
				785					790					795

&lt;210&gt; 15

&lt;211&gt; 393

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; misc\_feature

&lt;223&gt; Incyte ID No: 2182085CD1

&lt;400&gt; 15

Met	Glu	Asp	Phe	Glu	Asp	Asp	Pro	Arg	Ala	Leu	Gly	Ala	Arg	Gly
1				5					10					15
His	Arg	Arg	Ser	Val	Ser	Arg	Gly	Ser	Tyr	Gln	Leu	Gln	Ala	Gln
				20					25					30
Met	Asn	Arg	Ala	Val	Tyr	Glu	Asp	Arg	Pro	Pro	Gly	Ser	Val	Val
				35					40					45
Pro	Thr	Ser	Ala	Ala	Glu	Ala	Ser	Arg	Ala	Met	Ala	Gly	Asp	Thr
				50					55					60
Ser	Leu	Ser	Glu	Asn	Tyr	Ala	Phe	Ala	Gly	Met	Tyr	His	Val	Phe
				65					70					75
Asp	Gln	His	Val	Asp	Glu	Ala	Val	Pro	Arg	Val	Arg	Phe	Ala	Asn
				80					85					90
Asp	Asp	Arg	His	Arg	Leu	Ala	Cys	Cys	Ser	Leu	Asp	Gly	Ser	Ile
				95					100					105
Ser	Leu	Cys	Gln	Leu	Val	Pro	Ala	Pro	Pro	Thr	Val	Leu	Arg	Val
				110					115					120
Leu	Arg	Gly	His	Thr	Arg	Gly	Val	Ser	Asp	Phe	Ala	Trp	Ser	Leu
				125					130					135
Ser	Asn	Asp	Ile	Leu	Val	Ser	Thr	Ser	Leu	Asp	Ala	Thr	Met	Arg
				140					145					150

Ile Trp Ala Ser Glu Asp Gly Arg Cys Ile Arg Glu Ile Pro Asp  
 155 160 165  
 Pro Asp Ser Ala Glu Leu Leu Cys Cys Thr Phe Gln Pro Val Asn  
 170 175 180  
 Asn Asn Leu Thr Val Val Gly Asn Ala Lys His Asn Val His Val  
 185 190 195  
 Met Asn Ile Ser Thr Gly Lys Lys Val Lys Gly Gly Ser Ser Lys  
 200 205 210  
 Leu Thr Gly Arg Val Leu Ala Leu Ser Phe Asp Ala Pro Gly Arg  
 215 220 225  
 Leu Leu Trp Ala Gly Asp Asp Arg Gly Ser Val Phe Ser Phe Leu  
 230 235 240  
 Phe Asp Met Ala Thr Gly Lys Leu Thr Lys Ala Lys Arg Leu Val  
 245 250 255  
 Val His Glu Gly Ser Pro Val Thr Ser Ile Ser Ala Arg Ser Trp  
 260 265 270  
 Val Ser Arg Glu Ala Arg Asp Pro Ser Leu Leu Ile Asn Ala Cys  
 275 280 285  
 Leu Asn Lys Leu Leu Leu Tyr Arg Val Val Asp Asn Glu Gly Thr  
 290 295 300  
 Leu Gln Leu Lys Arg Ser Phe Pro Ile Glu Gln Ser Ser His Pro  
 305 310 315  
 Val Arg Ser Ile Phe Cys Pro Leu Met Ser Phe Arg Gln Gly Ala  
 320 325 330  
 Cys Val Val Thr Gly Ser Glu Asp Met Cys Val His Phe Phe Asp  
 335 340 345  
 Val Glu Arg Ala Ala Lys Ala Ala Val Asn Lys Leu Gln Gly His  
 350 355 360  
 Ser Ala Pro Val Leu Asp Val Ser Phe Asn Cys Asp Glu Ser Leu  
 365 370 375  
 Leu Ala Ser Ser Asp Ala Ser Gly Met Val Ile Val Trp Arg Arg  
 380 385 390  
 Glu Gln Lys

&lt;210&gt; 16

&lt;211&gt; 485

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; misc\_feature

&lt;223&gt; Incyte ID No: 2216640CD1

&lt;400&gt; 16

Met Ala Ala Ala Val Ala Asp Glu Ala Val Ala Arg Asp Val Gln  
 1 5 10 15  
 Arg Leu Leu Val Gln Phe Gln Asp Glu Gly Gly Gln Leu Leu Gly  
 20 25 30  
 Ser Pro Phe Asp Val Pro Val Asp Ile Thr Pro Asp Arg Leu Gln  
 35 40 45  
 Leu Val Cys Asn Ala Leu Leu Ala Gln Glu Asp Pro Leu Pro Leu  
 50 55 60  
 Ala Phe Phe Val His Asp Ala Glu Ile Val Ser Ser Leu Gly Lys  
 65 70 75  
 Thr Leu Glu Ser Gln Ala Val Glu Thr Glu Lys Val Leu Asp Ile  
 80 85 90  
 Ile Tyr Gln Pro Gln Ala Ile Phe Arg Val Arg Ala Val Thr Arg  
 95 100 105  
 Cys Thr Ser Ser Leu Glu Gly His Ser Glu Ala Val Ile Ser Val  
 110 115 120  
 Ala Phe Ser Pro Thr Gly Lys Tyr Leu Ala Ser Gly Ser Gly Asp  
 125 130 135  
 Thr Thr Val Arg Phe Trp Asp Leu Ser Thr Glu Thr Pro His Phe

Thr Cys Lys Gly	140	145	150
His Arg His Trp Val	155	160	165
Pro Asp Gly Lys	170	175	180
Leu Leu Trp Asp	185	190	195
Ala Gly His Ser	200	205	210
His Ala Asn Pro	215	220	225
Gly Ser Val Arg	230	235	240
Ile Leu Thr Gly	245	250	255
Gly Asp Gly Leu	260	265	270
Val Trp Arg Ala	275	280	285
His Gly His Trp	290	295	300
Leu Arg Thr Gly	305	310	315
Gln Asp Leu Gln	320	325	330
Ser Arg Tyr Asn	335	340	345
Ser Gly Ser Asp	350	355	360
Asp Lys Lys Pro	365	370	375
Asn Gln Val Leu	380	385	390
Ser Phe Asp Lys	395	400	405
Tyr Leu Ala Ser	410	415	420
Ala Trp Ser Ala	425	430	435
Ser Thr Leu Lys	440	445	450
Asp Leu Pro Gly	455	460	465
Pro Asp Gly Gln	470	475	480
Arg Ile Trp Arg	485		

&lt;210&gt; 17

&lt;211&gt; 199

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; misc\_feature

&lt;223&gt; Incyte ID No: 2417361CD1

&lt;400&gt; 17

Met Asn Pro Arg Lys	Lys Val Asp Leu Lys	Leu Ile Ile Val Gly
1	5	10
Ala Ile Gly Val Gly	Lys Thr Ser Leu Leu	His Gln Tyr Val His
20	25	30
Lys Thr Phe Tyr Glu	Glu Tyr Gln Thr Thr	Leu Gly Ala Ser Ile
35	40	45

Leu	Ser	Lys	Ile	Ile	Ile	Leu	Gly	Asp	Thr	Thr	Leu	Lys	Leu	Gln	
				50					55					60	
Ile	Trp	Asp	Thr	Gly	Gly	Gln	Glu	Arg	Phe	Arg	Ser	Met	Val	Ser	
				65					70					75	
Thr	Phe	Tyr	Lys	Gly	Ser	Asp	Gly	Cys	Ile	Leu	Ala	Phe	Asp	Val	
				80					85					90	
Thr	Asp	Leu	Glu	Ser	Phe	Glu	Ala	Leu	Asp	Ile	Trp	Arg	Gly	Asp	
				95					100					105	
Val	Leu	Ala	Lys	Ile	Val	Pro	Met	Glu	Gln	Ser	Tyr	Pro	Met	Val	
				110					115					120	
Leu	Leu	Gly	Asn	Lys	Ile	Asp	Leu	Ala	Asp	Arg	Lys	Val	Pro	Gln	
				125					130					135	
Glu	Val	Ala	Gln	Gly	Trp	Cys	Arg	Glu	Lys	Asp	Ile	Pro	Tyr	Phe	
				140					145					150	
Glu	Val	Ser	Ala	Lys	Asn	Asp	Ile	Asn	Val	Val	Gln	Ala	Phe	Glu	
				155					160					165	
Met	Leu	Ala	Ser	Arg	Ala	Leu	Ser	Arg	Tyr	Gln	Ser	Ile	Leu	Glu	
				170					175					180	
Asn	His	Leu	Thr	Glu	Ser	Ile	Lys	Leu	Ser	Pro	Asp	Gln	Ser	Arg	
				185					190					195	

Ser Arg Cys Cys

&lt;210&gt; 18

&lt;211&gt; 163

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; misc\_feature

&lt;223&gt; Incyte ID No: 2454384CD1

&lt;400&gt; 18

Met	Glu	Gly	Pro	Ser	Leu	Arg	Gly	Pro	Ala	Leu	Arg	Leu	Ala	Gly	
1				5					10					15	
Leu	Pro	Thr	Gln	Gln	Asp	Cys	Asn	Ile	Gln	Glu	Lys	Ile	Asp	Leu	
				20					25					30	
Glu	Ile	Arg	Met	Arg	Glu	Gly	Ile	Trp	Lys	Leu	Leu	Ser	Leu	Ser	
				35					40					45	
Thr	Gln	Lys	Asp	Gln	Val	Leu	His	Ala	Val	Lys	Asn	Leu	Met	Val	
				50					55					60	
Cys	Asn	Ala	Arg	Leu	Met	Ala	Tyr	Thr	Ser	Glu	Leu	Gln	Lys	Leu	
				65					70					75	
Glu	Glu	Gln	Ile	Ala	Asn	Gln	Thr	Gly	Arg	Cys	Asp	Val	Lys	Phe	
				80					85					90	
Glu	Ser	Lys	Glu	Arg	Thr	Ala	Cys	Lys	Gly	Lys	Ile	Ala	Ile	Ser	
				95					100					105	
Asp	Ile	Arg	Ile	Pro	Leu	Met	Trp	Lys	Asp	Ser	Asp	His	Phe	Ser	
				110					115					120	
Asn	Lys	Glu	Arg	Ser	Arg	Arg	Tyr	Ala	Ile	Phe	Cys	Leu	Phe	Lys	
				125					130					135	
Met	Gly	Ala	Asn	Val	Phe	Asp	Thr	Asp	Val	Val	Asn	Val	Asp	Lys	
				140					145					150	
Thr	Ile	Thr	Asp	Ile	Cys	Phe	Glu	Asn	Val	Thr	Ile	Leu			
				155					160						

&lt;210&gt; 19

&lt;211&gt; 290

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; misc\_feature

&lt;223&gt; Incyte ID No: 2610262CD1

&lt;400&gt; 19

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Met Ala Ala Glu Ile Gln Pro Lys Pro Leu Thr Arg Lys Pro Ile
 1      5      10
Leu Leu Gln Arg Met Glu Gly Ser Gln Glu Val Val Asn Met Ala
 20      25      30
Val Ile Val Pro Lys Glu Glu Gly Val Ile Ser Val Ser Glu Asp
 35      40      45
Arg Thr Val Arg Val Trp Leu Lys Arg Asp Ser Gly Gln Tyr Trp
 50      55      60
Pro Ser Val Tyr His Ala Met Pro Ser Pro Cys Ser Cys Met Ser
 65      70      75
Phe Asn Pro Glu Thr Arg Arg Leu Ser Ile Gly Leu Asp Asn Gly
 80      85      90
Thr Ile Ser Glu Phe Ile Leu Ser Glu Asp Tyr Asn Lys Met Thr
 95     100     105
Pro Val Lys Asn Tyr Gln Ala His Gln Ser Arg Val Thr Met Ile
110     115     120
Leu Phe Val Leu Glu Leu Glu Trp Val Leu Ser Thr Gly Gln Asp
125     130     135
Lys Gln Phe Ala Trp His Cys Ser Glu Ser Gly Gln Arg Leu Gly
140     145     150
Gly Tyr Arg Thr Ser Ala Val Ala Ser Gly Leu Gln Phe Asp Val
155     160     165
Glu Thr Arg His Val Phe Ile Gly Asp His Ser Gly Gln Val Thr
170     175     180
Ile Leu Lys Leu Glu Gln Glu Asn Cys Thr Leu Val Thr Thr Phe
185     190     195
Arg Gly His Thr Gly Gly Val Thr Ala Leu Cys Trp Asp Pro Val
200     205     210
Gln Arg Val Leu Phe Ser Gly Ser Ser Asp His Ser Val Ile Met
215     220     225
Trp Asp Ile Gly Gly Arg Lys Gly Thr Ala Ile Glu Leu Gln Gly
230     235     240
His Asn Asp Arg Val Gln Ala Leu Ser Tyr Ala Gln His Thr Arg
245     250     255
Gln Leu Ile Ser Cys Gly Gly Asp Gly Gly Ile Val Val Trp Asn
260     265     270
Met Asp Val Glu Arg Gln Glu Pro Leu Trp Ser Cys Phe Val Val
275     280     285
Met Ile Ser Ala Val
290

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&lt;210&gt; 20

&lt;211&gt; 705

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; misc\_feature

&lt;223&gt; Incyte ID No: 2700075CD1

&lt;400&gt; 20

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Met Gly Thr Trp Glu His Leu Val Ser Thr Gly Phe Asn Gln Met
 1      5      10
Arg Glu Arg Glu Val Lys Leu Trp Asp Thr Arg Phe Phe Ser Ser
 20      25      30
Ala Leu Ala Ser Leu Thr Leu Asp Thr Ser Leu Gly Cys Leu Val
 35      40      45
Pro Leu Leu Asp Pro Asp Ser Gly Leu Leu Val Leu Ala Gly Lys
 50      55      60
Gly Glu Arg Gln Leu Tyr Cys Tyr Glu Val Val Pro Gln Gln Pro
 65      70      75
Ala Leu Ser Pro Val Thr Gln Cys Val Leu Glu Ser Val Leu Arg
 80      85      90

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Gly	Ala	Ala	Leu	Val	Pro	Arg	Gln	Ala	Leu	Ala	Val	Met	Ser	Cys	
				95					100						105
Glu	Val	Leu	Arg	Val	Leu	Gln	Leu	Ser	Asp	Thr	Ala	Ile	Val	Pro	
				110					115						120
Ile	Gly	Tyr	His	Val	Pro	Arg	Lys	Ala	Val	Glu	Phe	His	Glu	Asp	
				125					130						135
Leu	Phe	Pro	Asp	Thr	Ala	Gly	Cys	Val	Pro	Ala	Thr	Asp	Pro	His	
				140					145						150
Ser	Trp	Trp	Ala	Gly	Asp	Asn	Gln	Gln	Val	Gln	Lys	Val	Ser	Leu	
				155					160						165
Asn	Pro	Ala	Cys	Arg	Pro	His	Pro	Ser	Phe	Thr	Ser	Cys	Leu	Val	
				170					175						180
Pro	Pro	Ala	Glu	Pro	Leu	Pro	Asp	Thr	Ala	Gln	Pro	Ala	Val	Met	
				185					190						195
Glu	Thr	Pro	Val	Gly	Asp	Ala	Asp	Ala	Ser	Glu	Gly	Phe	Ser	Ser	
				200					205						210
Pro	Pro	Ser	Ser	Leu	Thr	Ser	Pro	Ser	Thr	Pro	Ser	Ser	Leu	Gly	
				215					220						225
Pro	Ser	Leu	Ser	Ser	Thr	Ser	Gly	Ile	Gly	Thr	Ser	Pro	Ser	Leu	
				230					235						240
Arg	Ser	Leu	Gln	Ser	Leu	Leu	Gly	Pro	Ser	Ser	Lys	Phe	Arg	His	
				245					250						255
Ala	Gln	Gly	Thr	Val	Leu	His	Arg	Asp	Ser	His	Ile	Thr	Asn	Leu	
				260					265						270
Lys	Gly	Leu	Asn	Leu	Thr	Thr	Pro	Gly	Glu	Ser	Asp	Gly	Phe	Cys	
				275					280						285
Ala	Asn	Lys	Leu	Arg	Val	Ala	Val	Pro	Leu	Leu	Ser	Ser	Gly	Gly	
				290					295						300
Gln	Val	Ala	Val	Leu	Glu	Leu	Arg	Lys	Pro	Gly	Arg	Leu	Pro	Asp	
				305					310						315
Thr	Ala	Leu	Pro	Thr	Leu	Gln	Asn	Gly	Ala	Ala	Val	Thr	Asp	Leu	
				320					325						330
Ala	Trp	Asp	Pro	Phe	Asp	Pro	His	Arg	Leu	Ala	Val	Ala	Gly	Glu	
				335					340						345
Asp	Ala	Arg	Ile	Arg	Leu	Trp	Arg	Val	Pro	Ala	Glu	Gly	Leu	Glu	
				350					355						360
Glu	Val	Leu	Thr	Thr	Pro	Glu	Thr	Val	Leu	Thr	Gly	His	Thr	Glu	
				365					370						375
Lys	Ile	Cys	Ser	Leu	Arg	Phe	His	Pro	Leu	Ala	Ala	Asn	Val	Leu	
				380					385						390
Ala	Ser	Ser	Ser	Tyr	Asp	Leu	Thr	Val	Arg	Ile	Trp	Asp	Leu	Gln	
				395					400						405
Ala	Gly	Ala	Asp	Arg	Leu	Lys	Leu	Gln	Gly	His	Gln	Asp	Gln	Ile	
				410					415						420
Phe	Ser	Leu	Ala	Trp	Ser	Pro	Asp	Gly	Gln	Gln	Leu	Ala	Thr	Val	
				425					430						435
Cys	Lys	Asp	Gly	Arg	Val	Arg	Val	Tyr	Arg	Pro	Arg	Ser	Gly	Pro	
				440					445						450
Glu	Pro	Leu	Gln	Glu	Gly	Pro	Gly	Pro	Lys	Gly	Gly	Arg	Gly	Ala	
				455					460						465
Arg	Ile	Val	Trp	Val	Cys	Asp	Gly	Arg	Cys	Leu	Leu	Val	Ser	Gly	
				470					475						480
Phe	Asp	Ser	Gln	Ser	Glu	Arg	Gln	Leu	Leu	Leu	Tyr	Glu	Ala	Glu	
				485					490						495
Ala	Leu	Ala	Gly	Gly	Pro	Leu	Ala	Val	Leu	Gly	Leu	Asp	Val	Ala	
				500					505						510
Pro	Ser	Thr	Leu	Leu	Pro	Ser	Tyr	Asp	Pro	Asp	Thr	Gly	Leu	Val	
				515					520						525
Leu	Leu	Thr	Gly	Lys	Gly	Asp	Thr	Arg	Val	Phe	Leu	Tyr	Glu	Leu	
				530					535						540
Leu	Pro	Glu	Ser	Pro	Phe	Phe	Leu	Glu	Cys	Asn	Ser	Phe	Thr	Ser	
				545					550						555
Pro	Asp	Pro	His	Lys	Gly	Leu	Val	Leu	Leu	Pro	Lys	Thr	Glu	Cys	

Asp Val Arg Glu	560	Val Glu Leu Met Arg	565	Cys Leu Arg Leu Arg	570
	575		580		585
Ser Ser Leu Glu	590	Pro Val Ala Phe Arg	595	Leu Pro Arg Val Arg	600
Glu Phe Phe Gln	605	Asp Asp Val Phe Pro	610	Asp Thr Ala Val Ile	615
Glu Pro Val Leu	620	Ser Ala Glu Ala Trp	625	Leu Gln Gly Ala Asn	630
Gln Pro Trp Leu	635	Leu Ser Leu Gln Pro	640	Pro Asp Met Ser Pro	645
Ser Gln Ala Pro	650	Arg Glu Ala Pro Ala	655	Arg Arg Ala Pro Ser	660
Ala Gln Tyr Leu	665	Glu Glu Lys Ser Asp	670	Gln Gln Lys Lys Glu	675
Leu Leu Asn Ala	680	Met Val Ala Lys Leu	685	Gly Asn Arg Glu Asp	690
Leu Pro Gln Asp	695	Ser Phe Glu Gly Val	700	Asp Glu Asp Glu Trp	705

&lt;210&gt; 21

&lt;211&gt; 454

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; misc\_feature

&lt;223&gt; Incyte ID No: 2786701CD1

&lt;400&gt; 21

Met Ala Ser Ser	1	Glu Val Ala Arg His	10	Leu Leu Phe Gln Ser	15
	5		10		15
Met Ala Thr Lys	20	Thr Cys Met Ser	25	Gln Gly Ser Asp	30
	20		25		30
Glu Gln Ile Lys	35	Arg Glu Asn Ile Arg	40	Ser Leu Thr Met	45
	35		40		45
His Val Gly Phe	50	Glu Ser Leu Pro Asp	55	Gln Leu Val Asn	60
	50		55		60
Ile Gln Gln Gly	65	Phe Cys Phe Asn Ile	70	Leu Cys Val Gly	75
	65		70		75
Gly Ile Gly Lys	80	Ser Thr Leu Ile Asp	85	Thr Leu Phe Asn	90
	80		85		90
Phe Glu Asp Tyr	95	Glu Ser Ser His Phe	100	Cys Pro Asn Val	105
	95		100		105
Lys Ala Gln Thr	110	Tyr Glu Leu Gln Glu	115	Ser Asn Val Gln	120
	110		115		120
Leu Thr Ile Val	125	Asn Thr Val Gly Phe	130	Gly Asp Gln Ile	135
	125		130		135
Glu Glu Ser Tyr	140	Gln Pro Ile Val Asp	145	Tyr Ile Asp Ala	150
	140		145		150
Glu Ala Tyr Leu	155	Gln Glu Glu Leu Lys	160	Ile Lys Arg Ser	165
	155		160		165
Thr Tyr His Asp	170	Ser Arg Ile His Val	175	Cys Leu Tyr Phe	180
	170		175		180
Pro Thr Gly His	185	Ser Leu Lys Thr Leu	190	Asp Leu Leu Thr	195
	185		190		195
Asn Leu Asp Ser	200	Lys Val Asn Ile Ile	205	Pro Val Ile Ala	210
	200		205		210
Asp Thr Val Ser	215	Lys Thr Glu Leu Gln	220	Lys Phe Lys Ile	225
	215		220		225
Met Ser Glu Leu	230	Val Ser Asn Gly Val	235	Gln Ile Tyr Gln	240
	230		235		240
Thr Asp Asp Asp		Thr Ile Ala Lys Val		Asn Ala Ala Met	



Gln	Leu	Pro	Phe	245	Val	Val	Gly	Ser	250	Met	Asp	Glu	Val	Lys	255	Val
				260					265						270	
Gly	Asn	Lys	Met	275	Val	Lys	Ala	Arg	280	Gln	Tyr	Pro	Trp	Gly	285	Val
				290					295						300	
Gln	Val	Glu	Asn	305	Glu	Asn	His	Cys	310	Asp	Phe	Val	Lys	Leu	315	Arg
				320					325						330	
Met	Leu	Ile	Cys	335	Thr	Asn	Met	Glu	340	Asp	Leu	Arg	Glu	Gln	345	Thr
				350					355						360	
Thr	Arg	His	Tyr	365	Glu	Leu	Tyr	Arg	370	Arg	Cys	Lys	Leu	Glu	375	Met
				380					385						390	
Gly	Phe	Thr	Asp	395	Val	Gly	Pro	Glu	400	Asn	Lys	Pro	Val	Ser	405	Gln
				410					415						420	
Glu	Thr	Tyr	Glu	425	Ala	Lys	Arg	His	430	Glu	Phe	His	Gly	Glu	435	Arg
				440					445						450	
Arg	Lys	Glu	Glu		Glu	Met	Lys	Gln		Met	Phe	Val	Gln	Arg		Lys
Glu	Lys	Glu	Ala		Ile	Leu	Lys	Glu		Ala	Glu	Arg	Glu	Leu		Gln
Lys	Phe	Glu	His		Leu	Lys	Arg	Leu		His	Gln	Glu	Glu	Arg		Met
Leu	Glu	Glu	Lys		Arg	Leu	Leu	Glu		Glu	Glu	Ile	Ile	Ala		Phe
Ser	Lys	Lys	Lys		Ala	Thr	Ser	Glu		Ile	Phe	His	Ser	Gln		Ser
Leu	Ala	Thr	Gly		Ser	Asn	Leu	Arg		Lys	Asp	Lys	Asp	Arg		Lys
Ser	Asn	Phe	Leu													

&lt;210&gt; 22

&lt;211&gt; 433

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; misc\_feature

&lt;223&gt; Incyte ID No: 3068538CD1

&lt;400&gt; 22

Met	Ala	Gly	Gln	Asp	Pro	Ala	Leu	Ser	Thr	Ser	His	Pro	Phe	Tyr
1				5					10					15
Asp	Val	Ala	Arg	His	Gly	Ile	Leu	Gln	Val	Ala	Gly	Asp	Asp	Arg
				20					25					30
Phe	Gly	Arg	Arg	Val	Val	Thr	Phe	Ser	Cys	Cys	Arg	Met	Pro	Pro
				35					40					45
Ser	His	Glu	Leu	Asp	His	Gln	Arg	Leu	Leu	Glu	Tyr	Leu	Lys	Tyr
				50					55					60
Thr	Leu	Asp	Gln	Tyr	Val	Glu	Asn	Asp	Tyr	Thr	Ile	Val	Tyr	Phe
				65					70					75
His	Tyr	Gly	Leu	Asn	Ser	Arg	Asn	Lys	Pro	Ser	Leu	Gly	Trp	Leu
				80					85					90
Gln	Ser	Ala	Tyr	Lys	Glu	Phe	Asp	Arg	Lys	Tyr	Lys	Lys	Asn	Leu
				95					100					105
Lys	Ala	Leu	Tyr	Val	Val	His	Pro	Thr	Ser	Phe	Ile	Lys	Val	Leu
				110					115					120
Trp	Asn	Ile	Leu	Lys	Pro	Leu	Ile	Ser	His	Lys	Phe	Gly	Lys	Lys
				125					130					135
Val	Ile	Tyr	Phe	Asn	Tyr	Leu	Ser	Glu	Leu	His	Glu	His	Leu	Lys
				140					145					150
Tyr	Asp	Gln	Leu	Val	Ile	Pro	Pro	Glu	Val	Leu	Arg	Tyr	Asp	Glu
				155					160					165
Lys	Leu	Gln	Ser	Leu	His	Glu	Gly	Arg	Thr	Pro	Pro	Pro	Thr	Lys
				170					175					180

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Thr Pro Pro Pro Arg Pro Pro Leu Pro Thr Gln Gln Phe Gly Val
185 190
Ser Leu Gln Tyr Leu Lys Asp Lys Asn Gln Gly Glu Leu Ile Pro
200 205
Pro Val Leu Arg Phe Thr Val Thr Tyr Leu Arg Glu Lys Gly Leu
215 220
Arg Thr Glu Gly Leu Phe Arg Arg Ser Ala Ser Val Gln Thr Val
230 235
Arg Glu Ile Gln Arg Leu Tyr Asn Gln Gly Lys Pro Val Asn Phe
245 250
Asp Asp Tyr Gly Asp Ile His Ile Pro Ala Val Ile Leu Lys Thr
260 265
Phe Leu Arg Glu Leu Pro Gln Pro Leu Leu Thr Phe Gln Ala Tyr
275 280
Glu Gln Ile Leu Gly Ile Thr Cys Val Glu Ser Ser Leu Arg Val
290 295
Thr Gly Cys Arg Gln Ile Leu Arg Ser Leu Pro Glu His Asn Tyr
305 310
Val Val Leu Arg Tyr Leu Met Gly Phe Leu His Ala Val Ser Arg
320 325
Glu Ser Ile Phe Asn Lys Met Asn Ser Ser Asn Leu Ala Cys Val
335 340
Phe Gly Leu Asn Leu Ile Trp Pro Ser Gln Gly Val Ser Ser Leu
350 355
Ser Ala Leu Val Pro Leu Asn Met Phe Thr Glu Leu Leu Ile Glu
365 370
Tyr Tyr Glu Lys Ile Phe Ser Thr Pro Glu Ala Pro Gly Glu His
380 385
Gly Leu Ala Pro Trp Glu Gln Gly Ser Arg Ala Ala Pro Leu Gln
395 400
Glu Ala Val Pro Arg Thr Gln Ala Thr Gly Leu Thr Lys Pro Thr
410 415
Leu Pro Pro Ser Pro Leu Met Ala Ala Arg Arg Arg Leu
425 430

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&lt;210&gt; 23

&lt;211&gt; 406

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; misc\_feature

&lt;223&gt; Incyte ID No: 5159072CD1

&lt;400&gt; 23

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Met Ala Asp Gly Asn Glu Asp Leu Arg Ala Asp Asp Leu Pro Gly
1 5 10 15
Pro Ala Phe Glu Ser Tyr Glu Ser Met Glu Leu Ala Cys Pro Ala
20 25 30
Glu Arg Ser Gly His Val Ala Val Ser Asp Gly Arg His Met Phe
35 40 45
Val Trp Gly Gly Tyr Lys Ser Asn Gln Val Arg Gly Leu Tyr Asp
50 55 60
Phe Tyr Leu Pro Arg Glu Glu Leu Trp Ile Tyr Asn Met Glu Thr
65 70 75
Gly Arg Trp Lys Lys Ile Asn Thr Glu Gly Asp Val Pro Pro Ser
80 85 90
Met Ser Gly Ser Cys Ala Val Cys Val Asp Arg Val Leu Tyr Leu
95 100 105
Phe Gly Gly His His Ser Arg Gly Asn Thr Asn Lys Phe Tyr Met
110 115 120
Leu Asp Ser Arg Ser Thr Asp Arg Val Leu Gln Trp Glu Arg Ile
125 130 135
Asp Cys Gln Gly Ile Pro Pro Ser Ser Lys Asp Lys Leu Gly Val

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	140		145		150
Trp Val Tyr Lys	Asn Lys Leu Ile Phe	Phe Gly Gly Tyr Gly Tyr			
	155	160			165
Leu Pro Glu Asp	Lys Val Leu Gly Thr	Phe Glu Phe Asp Glu Thr			
	170	175			180
Ser Phe Trp Asn	Ser Ser His Pro Arg	Gly Trp Asn Asp His Val			
	185	190			195
His Ile Leu Asp	Thr Glu Thr Phe Thr	Trp Ser Gln Pro Ile Thr			
	200	205			210
Thr Gly Lys Ala	Pro Ser Pro Arg Ala	Ala His Ala Cys Ala Thr			
	215	220			225
Val Gly Asn Arg	Gly Phe Val Phe Gly	Gly Arg Tyr Arg Asp Ala			
	230	235			240
Arg Met Asn Asp	Leu His Tyr Leu Asn	Leu Asp Thr Trp Glu Trp			
	245	250			255
Asn Glu Leu Ile	Pro Gln Gly Ile Cys	Pro Val Gly Arg Ser Trp			
	260	265			270
His Ser Leu Thr	Pro Val Ser Ser Asp	His Leu Phe Leu Phe Gly			
	275	280			285
Gly Phe Thr Thr	Asp Lys Gln Pro Leu	Ser Asp Ala Trp Thr Tyr			
	290	295			300
Cys Ile Ser Lys	Asn Glu Trp Ile Gln	Phe Asn His Pro Tyr Thr			
	305	310			315
Glu Lys Pro Arg	Leu Trp His Thr Ala	Cys Ala Ser Asp Glu Gly			
	320	325			330
Glu Val Ile Val	Phe Gly Gly Cys Ala	Asn Asn Leu Leu Val His			
	335	340			345
His Arg Ala Ala	His Ser Asn Glu Ile	Leu Ile Phe Ser Val Gln			
	350	355			360
Pro Lys Ser Leu	Val Arg Leu Ser Leu	Glu Ala Val Ile Cys Phe			
	365	370			375
Lys Glu Met Leu	Ala Asn Ser Trp Asn	Cys Leu Pro Lys His Leu			
	380	385			390
Leu His Ser Val	Asn Gln Arg Phe Gly	Ser Asn Asn Thr Ser Gly			
	395	400			405

Ser

&lt;210&gt; 24

&lt;211&gt; 229

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; misc\_feature

&lt;223&gt; Incyte ID No: 5519057CD1

&lt;400&gt; 24

Met Ala Glu Glu Met	Glu Ser Ser Leu Glu	Ala Ser Phe Ser Ser	
1	5	10	15
Ser Gly Ala Val Ser	Gly Ala Ser Gly Phe	Leu Pro Pro Ala Arg	
	20	25	30
Ser Arg Ile Phe Lys	Ile Ile Val Ile Gly	Asp Ser Asn Val Gly	
	35	40	45
Lys Thr Cys Leu Thr	Tyr Arg Phe Cys Ala	Gly Arg Phe Pro Asp	
	50	55	60
Arg Thr Glu Ala Thr	Ile Gly Val Asp Phe	Arg Glu Arg Ala Val	
	65	70	75
Glu Ile Asp Gly Glu	Arg Ile Lys Ile Gln	Leu Trp Asp Thr Ala	
	80	85	90
Gly Gln Glu Arg Phe	Arg Lys Ser Met Val	Gln His Tyr Tyr Arg	
	95	100	105
Asn Val His Ala Val	Val Phe Val Tyr Asp	Met Thr Asn Met Ala	
	110	115	120

Ser Phe His Ser Leu Pro Ser Trp Ile Glu Glu Cys Lys Gln His  
 125 130 135  
 Leu Leu Ala Asn Asp Ile Pro Arg Ile Leu Val Gly Asn Lys Cys  
 140 145 150  
 Asp Leu Arg Ser Ala Ile Gln Val Pro Thr Asp Leu Ala Gln Lys  
 155 160 165  
 Phe Ala Asp Thr His Ser Met Pro Leu Phe Glu Thr Ser Ala Lys  
 170 175 180  
 Asn Pro Asn Asp Asn Asp His Val Glu Ala Ile Phe Met Thr Leu  
 185 190 195  
 Ala His Lys Leu Lys Cys His Lys Pro Leu Met Leu Ser Gln Pro  
 200 205 210  
 Pro Asp Asn Gly Ile Ile Leu Lys Pro Glu Pro Lys Pro Ala Met  
 215 220 225  
 Thr Cys Trp Cys

&lt;210&gt; 25

&lt;211&gt; 670

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; misc\_feature

&lt;223&gt; Incyte ID No: 035379CD1

&lt;400&gt; 25

Met Ser Ser Gly Lys Ser Ala Arg Tyr Asn Arg Phe Ser Gly Gly  
 1 5 10 15  
 Pro Ser Asn Leu Pro Thr Pro Asp Val Thr Thr Gly Thr Arg Met  
 20 25 30  
 Glu Thr Thr Phe Gly Pro Ala Phe Ser Ala Val Thr Thr Ile Thr  
 35 40 45  
 Lys Ala Asp Gly Thr Ser Thr Tyr Lys Gln His Cys Arg Thr Pro  
 50 55 60  
 Ser Ser Ser Ser Thr Leu Ala Tyr Ser Pro Arg Asp Glu Glu Asp  
 65 70 75  
 Ser Met Pro Pro Ile Ser Thr Pro Arg Arg Ser Asp Ser Ala Ile  
 80 85 90  
 Ser Val Arg Ser Leu His Ser Glu Ser Ser Met Ser Leu Arg Ser  
 95 100 105  
 Thr Phe Ser Leu Pro Glu Glu Glu Glu Glu Pro Glu Pro Leu Val  
 110 115 120  
 Phe Ala Glu Gln Pro Ser Val Lys Leu Cys Cys Gln Leu Cys Cys  
 125 130 135  
 Ser Val Phe Lys Asp Pro Val Ile Thr Thr Cys Gly His Thr Phe  
 140 145 150  
 Cys Arg Arg Cys Ala Leu Lys Ser Glu Lys Cys Pro Val Asp Asn  
 155 160 165  
 Val Lys Leu Thr Val Val Val Asn Asn Ile Ala Val Ala Glu Gln  
 170 175 180  
 Ile Gly Glu Leu Phe Ile His Cys Arg His Gly Cys Arg Val Ala  
 185 190 195  
 Gly Ser Gly Lys Pro Pro Ile Phe Glu Val Asp Pro Arg Gly Cys  
 200 205 210  
 Pro Phe Thr Ile Lys Leu Ser Ala Arg Lys Asp His Glu Gly Ser  
 215 220 225  
 Cys Asp Tyr Arg Pro Val Arg Cys Pro Asn Asn Pro Ser Cys Pro  
 230 235 240  
 Pro Leu Leu Arg Met Asn Leu Glu Ala His Leu Lys Glu Cys Glu  
 245 250 255  
 His Ile Lys Cys Pro His Ser Lys Tyr Gly Cys Thr Phe Ile Gly  
 260 265 270  
 Asn Gln Asp Thr Tyr Glu Thr His Leu Glu Thr Cys Arg Phe Glu

	275	280	285
Gly Leu Lys Glu Phe Leu Gln Gln Thr	Asp Asp Arg Phe His	Glu	
	290	295	300
Met His Val Ala Leu Ala Gln Lys Asp	Gln Glu Ile Ala Phe	Leu	
	305	310	315
Arg Ser Met Leu Gly Lys Leu Ser Glu	Lys Ile Asp Gln Leu	Glu	
	320	325	330
Lys Ser Leu Glu Leu Lys Phe Asp Val	Leu Asp Glu Asn Gln	Ser	
	335	340	345
Lys Leu Ser Glu Asp Leu Met Glu Phe	Arg Arg Asp Ala Ser	Met	
	350	355	360
Leu Asn Asp Glu Leu Ser His Ile Asn	Ala Arg Leu Asn Met	Gly	
	365	370	375
Ile Leu Gly Ser Tyr Asp Pro Gln Gln	Ile Phe Lys Cys Lys	Gly	
	380	385	390
Thr Phe Val Gly His Gln Gly Pro Val	Trp Cys Leu Cys Val	Tyr	
	395	400	405
Ser Met Gly Asp Leu Leu Phe Ser Gly	Ser Ser Asp Lys Thr	Ile	
	410	415	420
Lys Val Trp Asp Thr Cys Thr Thr Tyr	Lys Cys Gln Lys Thr	Leu	
	425	430	435
Glu Gly His Asp Gly Ile Val Leu Ala	Leu Cys Ile Gln Gly	Cys	
	440	445	450
Lys Leu Tyr Ser Gly Ser Ala Asp Cys	Thr Ile Ile Val Trp	Asp	
	455	460	465
Ile Gln Asn Leu Gln Lys Val Asn Thr	Ile Arg Ala His Asp	Asn	
	470	475	480
Pro Val Cys Thr Leu Val Ser Ser His	Asn Val Leu Phe Ser	Gly	
	485	490	495
Ser Leu Lys Ala Ile Lys Val Trp Asp	Ile Val Gly Thr Glu	Leu	
	500	505	510
Lys Leu Lys Lys Glu Leu Thr Gly Leu	Asn His Trp Val Arg	Ala	
	515	520	525
Leu Val Ala Ala Gln Ser Tyr Leu Tyr	Ser Gly Ser Tyr Gln	Thr	
	530	535	540
Ile Lys Ile Trp Asp Ile Arg Thr Leu	Asp Cys Ile His Val	Leu	
	545	550	555
Gln Thr Ser Gly Gly Ser Val Tyr Ser	Ile Ala Val Thr Asn	His	
	560	565	570
His Ile Val Cys Gly Thr Tyr Glu Asn	Leu Ile His Val Trp	Asp	
	575	580	585
Ile Glu Ser Lys Glu Gln Val Arg Thr	Leu Thr Gly His Val	Gly	
	590	595	600
Thr Val Tyr Ala Leu Ala Val Ile Ser	Thr Pro Asp Gln Thr	Lys	
	605	610	615
Val Phe Ser Ala Ser Tyr Asp Arg Ser	Leu Arg Val Trp Ser	Met	
	620	625	630
Asp Asn Met Ile Cys Thr Gln Thr Leu	Leu Arg His Gln Ser	Ser	
	635	640	645
Val Thr Ala Leu Ala Val Ser Arg Gly	Arg Leu Phe Ser Gly	Ala	
	650	655	660
Val Asp Ser Thr Val Lys Val Trp Thr	Cys		
	665	670	

&lt;210&gt; 26

&lt;211&gt; 445

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; misc\_feature

&lt;223&gt; Incyte ID No: 275354CD1

&lt;400&gt; 26

Met	Lys	Val	Lys	Met	Leu	Ser	Arg	Asn	Pro	Asp	Asn	Tyr	Val	Arg
1				5					10					15
Glu	Thr	Lys	Leu	Asp	Leu	Gln	Arg	Val	Pro	Arg	Asn	Tyr	Asp	Pro
				20					25					30
Ala	Leu	His	Pro	Phe	Glu	Val	Pro	Arg	Glu	Tyr	Val	Arg	Ala	Leu
				35					40					45
Asn	Ala	Thr	Lys	Leu	Glu	Arg	Val	Phe	Ala	Lys	Pro	Phe	Leu	Ala
				50					55					60
Ser	Leu	Asp	Gly	His	Arg	Asp	Gly	Val	Asn	Cys	Leu	Ala	Lys	His
				65					70					75
Pro	Glu	Lys	Leu	Ala	Thr	Val	Leu	Ser	Gly	Ala	Cys	Asp	Gly	Glu
				80					85					90
Val	Arg	Ile	Trp	Asn	Leu	Thr	Gln	Arg	Asn	Cys	Ile	Arg	Thr	Ile
				95					100					105
Gln	Ala	His	Glu	Gly	Phe	Val	Arg	Gly	Ile	Cys	Thr	Arg	Phe	Cys
				110					115					120
Gly	Thr	Ser	Phe	Phe	Thr	Val	Gly	Asp	Asp	Lys	Thr	Val	Lys	Gln
				125					130					135
Trp	Lys	Met	Asp	Gly	Pro	Gly	Tyr	Gly	Asp	Glu	Glu	Glu	Pro	Leu
				140					145					150
His	Thr	Ile	Leu	Gly	Lys	Thr	Val	Tyr	Thr	Gly	Ile	Asp	His	His
				155					160					165
Trp	Lys	Glu	Ala	Val	Phe	Ala	Thr	Cys	Gly	Gln	Gln	Val	Asp	Ile
				170					175					180
Trp	Asp	Glu	Gln	Arg	Thr	Asn	Pro	Ile	Cys	Ser	Met	Thr	Trp	Gly
				185					190					195
Phe	Asp	Ser	Ile	Ser	Ser	Val	Lys	Phe	Asn	Pro	Ile	Glu	Thr	Phe
				200					205					210
Leu	Leu	Gly	Ser	Cys	Ala	Ser	Asp	Arg	Asn	Ile	Val	Leu	Tyr	Asp
				215					220					225
Met	Arg	Gln	Ala	Thr	Pro	Leu	Lys	Lys	Val	Ile	Leu	Asp	Met	Arg
				230					235					240
Thr	Asn	Thr	Ile	Cys	Trp	Asn	Pro	Met	Glu	Ala	Phe	Ile	Phe	Thr
				245					250					255
Ala	Ala	Asn	Glu	Asp	Tyr	Asn	Leu	Tyr	Thr	Phe	Asp	Met	Arg	Ala
				260					265					270
Leu	Asp	Thr	Pro	Val	Met	Val	His	Met	Asp	His	Val	Ser	Ala	Val
				275					280					285
Leu	Asp	Val	Asp	Tyr	Ser	Pro	Thr	Gly	Lys	Glu	Phe	Val	Ser	Ala
				290					295					300
Ser	Phe	Asp	Lys	Ser	Ile	Arg	Ile	Phe	Pro	Val	Asp	Lys	Ser	Arg
				305					310					315
Ser	Arg	Glu	Val	Tyr	His	Thr	Lys	Arg	Met	Gln	His	Val	Ile	Cys
				320					325					330
Val	Lys	Trp	Thr	Ser	Asp	Ser	Lys	Tyr	Ile	Met	Cys	Gly	Ser	Asp
				335					340					345
Glu	Met	Asn	Ile	Arg	Leu	Trp	Lys	Ala	Asn	Ala	Ser	Glu	Lys	Leu
				350					355					360
Gly	Val	Leu	Thr	Ser	Arg	Glu	Lys	Ala	Ala	Lys	Asp	Tyr	Asn	Gln
				365					370					375
Lys	Leu	Lys	Glu	Lys	Phe	Gln	His	Tyr	Pro	His	Ile	Lys	Arg	Ile
				380					385					390
Ala	Arg	His	Arg	His	Leu	Pro	Lys	Ser	Ile	Tyr	Ser	Gln	Ile	Gln
				395					400					405
Glu	Gln	Arg	Ile	Met	Lys	Glu	Ala	Arg	Arg	Arg	Lys	Glu	Val	Asn
				410					415					420
Arg	Ile	Lys	His	Ser	Lys	Pro	Gly	Ser	Val	Pro	Leu	Val	Ser	Glu
				425					430					435
Lys	Lys	Lys	His	Val	Val	Ala	Val	Val	Lys					
				440					445					

&lt;210&gt; 27

&lt;211&gt; 236

&lt;212&gt; PRT

<223> Incyte ID No: 311658CD1

Met	Ser	Asp	Leu	Leu	Ser	Pro	Leu	Leu	Tyr	Val	Met	Glu	Asn	Glu
1				5					10					15
Val	Asp	Ala	Phe	Trp	Cys	Phe	Ala	Ser	Tyr	Met	Asp	Gln	Met	His
				20					25					30
Gln	Asn	Phe	Glu	Glu	Gln	Met	Gln	Gly	Met	Lys	Thr	Gln	Leu	Ile
				35					40					45
Gln	Leu	Ser	Thr	Leu	Leu	Arg	Leu	Leu	Asp	Ser	Gly	Phe	Cys	Ser
				50					55					60
Tyr	Leu	Glu	Ser	Gln	Asp	Ser	Gly	Tyr	Leu	Tyr	Phe	Cys	Phe	Arg
				65					70					75
Trp	Leu	Leu	Ile	Arg	Phe	Lys	Arg	Glu	Phe	Ser	Phe	Leu	Asp	Ile
				80					85					90
Leu	Arg	Leu	Trp	Glu	Val	Met	Trp	Thr	Glu	Leu	Pro	Cys	Thr	Asn
				95					100					105
Phe	His	Leu	Leu	Leu	Cys	Cys	Ala	Ile	Leu	Glu	Ser	Glu	Lys	Gln
				110					115					120
Gln	Ile	Met	Glu	Lys	His	Tyr	Gly	Phe	Asn	Glu	Ile	Leu	Lys	His
				125					130					135
Ile	Asn	Glu	Leu	Ser	Met	Lys	Ile	Asp	Val	Glu	Asp	Ile	Leu	Cys
				140					145					150
Lys	Ala	Glu	Ala	Ile	Ser	Leu	Gln	Met	Val	Lys	Cys	Lys	Glu	Leu
				155					160					165
Pro	Gln	Ala	Val	Cys	Glu	Ile	Leu	Gly	Leu	Gln	Gly	Ser	Glu	Val
				170					175					180
Thr	Thr	Pro	Asp	Ser	Asp	Val	Gly	Glu	Asp	Glu	Asn	Val	Val	Met
				185					190					195
Thr	Pro	Cys	Pro	Thr	Ser	Ala	Phe	Gln	Ser	Asn	Ala	Leu	Pro	Thr
				200					205					210
Leu	Ser	Ala	Ser	Gly	Ala	Arg	Asn	Asp	Ser	Pro	Thr	Gln	Ile	Pro
				215					220					225
Val	Ser	Ser	Asp	Val	Cys	Arg	Leu	Thr	Pro	Ala				
				230					235					

<213> Homo sapiens

<223> Incyte ID No: 1251632CD1

Met	Gln	Glu	Ser	Gly	Cys	Arg	Leu	Glu	His	Pro	Ser	Ala	Thr	Lys
1				5					10					15
Phe	Arg	Asn	His	Val	Met	Glu	Gly	Asp	Trp	Asp	Lys	Ala	Glu	Asn
				20					25					30
Asp	Leu	Asn	Glu	Leu	Lys	Pro	Leu	Val	His	Ser	Pro	His	Ala	Ile
				35					40					45
Val	Arg	Met	Lys	Phe	Leu	Leu	Leu	Gln	Gln	Lys	Tyr	Leu	Glu	Tyr
				50					55					60
Leu	Glu	Asp	Gly	Lys	Val	Leu	Glu	Ala	Leu	Gln	Val	Leu	Arg	Cys
				65					70					75
Glu	Leu	Thr	Pro	Leu	Lys	Tyr	Asn	Thr	Glu	Arg	Ile	His	Val	Leu
				80					85					90
Ser	Gly	Tyr	Leu	Met	Cys	Ser	His	Ala	Glu	Asp	Leu	Arg	Ala	Lys
				95					100					105

Ala	Glu	Trp	Glu	Gly	Lys	Gly	Thr	Ala	Ser	Arg	Ser	Lys	Leu	Leu	
				110					115					120	
Asp	Lys	Leu	Gln	Thr	Tyr	Leu	Pro	Pro	Ser	Val	Met	Leu	Pro	Pro	
				125					130					135	
Arg	Arg	Leu	Gln	Thr	Leu	Leu	Arg	Gln	Ala	Val	Glu	Leu	Gln	Arg	
				140					145					150	
Asp	Arg	Cys	Leu	Tyr	His	Asn	Thr	Lys	Leu	Asp	Asn	Asn	Leu	Asp	
				155					160					165	
Ser	Val	Ser	Leu	Leu	Ile	Asp	His	Val	Cys	Ser	Arg	Arg	Gln	Phe	
				170					175					180	
Pro	Cys	Tyr	Thr	Gln	Gln	Ile	Leu	Thr	Glu	His	Cys	Asn	Glu	Val	
				185					190					195	
Trp	Phe	Cys	Lys	Phe	Ser	Asn	Asp	Gly	Thr	Lys	Leu	Ala	Thr	Gly	
				200					205					210	
Ser	Lys	Asp	Thr	Thr	Val	Ile	Ile	Trp	Gln	Val	Asp	Pro	Asp	Thr	
				215					220					225	
His	Leu	Leu	Lys	Leu	Leu	Lys	Thr	Leu	Glu	Gly	His	Ala	Tyr	Gly	
				230					235					240	
Val	Ser	Tyr	Ile	Ala	Trp	Ser	Pro	Asp	Asp	Asn	Tyr	Leu	Val	Ala	
				245					250					255	
Cys	Gly	Pro	Asp	Asp	Cys	Ser	Glu	Leu	Trp	Leu	Trp	Asn	Val	Gln	
				260					265					270	
Thr	Gly	Glu	Leu	Arg	Thr	Lys	Met	Ser	Gln	Ser	His	Glu	Asp	Ser	
				275					280					285	
Leu	Thr	Ser	Val	Ala	Trp	Asn	Pro	Asp	Gly	Lys	Arg	Phe	Val	Thr	
				290					295					300	
Gly	Gly	Gln	Arg	Gly	Gln	Phe	Tyr	Gln	Cys	Asp	Leu	Asp	Gly	Asn	
				305					310					315	
Leu	Leu	Asp	Ser	Trp	Glu	Gly	Val	Arg	Val	Gln	Cys	Leu	Trp	Cys	
				320					325					330	
Leu	Ser	Asp	Gly	Lys	Thr	Val	Leu	Ala	Ser	Asp	Thr	His	Gln	Arg	
				335					340					345	
Ile	Arg	Gly	Tyr	Asn	Phe	Glu	Asp	Leu	Thr	Asp	Arg	Asn	Ile	Val	
				350					355					360	
Gln	Glu	Asp	His	Pro	Ile	Met	Ser	Phe	Thr	Ile	Ser	Lys	Asn	Gly	
				365					370					375	
Arg	Leu	Ala	Leu	Leu	Asn	Val	Ala	Thr	Gln	Gly	Val	His	Leu	Trp	
				380					385					390	
Asp	Leu	Gln	Asp	Arg	Val	Leu	Val	Arg	Lys	Tyr	Gln	Gly	Val	Thr	
				395					400					405	
Gln	Gly	Phe	Tyr	Thr	Ile	His	Ser	Cys	Phe	Gly	Gly	His	Asn	Glu	
				410					415					420	
Asp	Phe	Ile	Ala	Ser	Gly	Ser	Glu	Asp	His	Lys	Val	Tyr	Ile	Trp	
				425					430					435	
His	Lys	Arg	Ser	Glu	Leu	Pro	Ile	Ala	Glu	Leu	Thr	Gly	His	Thr	
				440					445					450	
Arg	Thr	Val	Asn	Cys	Val	Ser	Trp	Asn	Pro	Gln	Ile	Pro	Ser	Met	
				455					460					465	
Met	Ala	Ser	Ala	Ser	Asp	Asp	Gly	Thr	Val	Arg	Ile	Trp	Gly	Pro	
				470					475					480	
Ala	Pro	Phe	Ile	Asp	His	Gln	Asn	Ile	Glu	Glu	Glu	Cys	Ser	Ser	
				485					490					495	

Met Asp Ser

&lt;210&gt; 29

&lt;211&gt; 334

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; misc\_feature

&lt;223&gt; Incyte ID No: 1331955CD1



&lt;400&gt; 29

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Met Ala Thr Glu Glu Lys Lys Pro Glu Thr Glu Ala Ala Arg Ala
1      5      10      15
Gln Pro Thr Pro Ser Ser Ser Ala Thr Gln Ser Lys Pro Thr Pro
20      25      30
Val Lys Pro Asn Tyr Ala Leu Lys Phe Thr Leu Ala Gly His Thr
35      40      45
Lys Ala Val Ser Ser Val Lys Phe Ser Pro Asn Gly Glu Trp Leu
50      55      60
Ala Ser Ser Ser Ala Asp Lys Leu Ile Lys Ile Trp Gly Ala Tyr
65      70      75
Asp Gly Lys Phe Glu Lys Thr Ile Ser Gly His Lys Leu Gly Ile
80      85      90
Ser Asp Val Ala Trp Ser Ser Asp Ser Asn Leu Leu Val Ser Ala
95      100     105
Ser Asp Asp Lys Thr Leu Lys Ile Trp Asp Val Ser Ser Gly Lys
110     115     120
Cys Leu Lys Thr Leu Lys Gly His Ser Asn Tyr Val Phe Cys Cys
125     130     135
Asn Phe Asn Pro Gln Ser Asn Leu Ile Val Ser Gly Ser Phe Asp
140     145     150
Glu Ser Val Arg Ile Trp Asp Val Lys Thr Gly Lys Cys Leu Lys
155     160     165
Thr Leu Pro Ala His Ser Asp Pro Val Ser Ala Val His Phe Asn
170     175     180
Arg Asp Gly Ser Leu Ile Val Ser Ser Ser Tyr Asp Gly Leu Cys
185     190     195
Arg Ile Trp Asp Thr Ala Ser Gly Gln Cys Leu Lys Thr Leu Ile
200     205     210
Asp Asp Asp Asn Pro Pro Val Ser Phe Val Lys Phe Ser Pro Asn
215     220     225
Gly Lys Tyr Ile Leu Ala Ala Thr Leu Asp Asn Thr Leu Lys Leu
230     235     240
Trp Asp Tyr Ser Lys Gly Lys Cys Leu Lys Thr Tyr Thr Gly His
245     250     255
Lys Asn Glu Lys Tyr Cys Ile Phe Ala Asn Phe Ser Val Thr Gly
260     265     270
Gly Lys Trp Ile Val Ser Gly Ser Glu Asp Asn Leu Val Tyr Ile
275     280     285
Trp Asn Leu Gln Thr Lys Glu Ile Val Gln Lys Leu Gln Gly His
290     295     300
Thr Asp Val Val Ile Ser Thr Ala Cys His Pro Thr Glu Asn Ile
305     310     315
Ile Ala Ser Ala Ala Leu Glu Asn Asp Lys Thr Ile Lys Leu Trp
320     325     330
Lys Ser Asp Cys

```

&lt;210&gt; 30

&lt;211&gt; 292

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; misc\_feature

&lt;223&gt; Incyte ID No: 1412614CD1

&lt;400&gt; 30

```

Met Met Ala Phe Ala Pro Pro Lys Asn Thr Asp Gly Pro Lys Met
1      5      10      15
Gln Thr Lys Met Ser Thr Trp Thr Pro Leu Asn His Gln Leu Leu
20      25      30
Asn Asp Arg Val Phe Glu Glu Arg Arg Ala Leu Leu Gly Lys Trp
35      40      45

```

Phe Asp Lys Trp Thr Asp Ser Gln Arg Arg Arg Ile Leu Thr Gly  
 50 55 60  
 Leu Leu Glu Arg Cys Ser Leu Ser Gln Gln Lys Phe Cys Cys Arg  
 65 70 75  
 Lys Leu Gln Glu Lys Ile Pro Ala Glu Ala Leu Asp Phe Thr Thr  
 80 85 90  
 Lys Leu Pro Arg Val Leu Ser Leu Tyr Ile Phe Ser Phe Leu Asp  
 95 100 105  
 Pro Arg Ser Leu Cys Arg Cys Ala Gln Val Cys Trp His Trp Lys  
 110 115 120  
 Asn Leu Ala Glu Leu Asp Gln Leu Trp Met Leu Lys Cys Leu Arg  
 125 130 135  
 Phe Asn Trp Tyr Ile Asn Phe Ser Pro Thr Pro Phe Glu Gln Gly  
 140 145 150  
 Ile Trp Lys Lys His Tyr Ile Gln Met Val Lys Glu Leu His Ile  
 155 160 165  
 Thr Lys Pro Lys Thr Pro Pro Lys Asp Gly Phe Val Ile Ala Asp  
 170 175 180  
 Val Gln Leu Val Thr Ser Asn Ser Pro Glu Glu Lys Gln Ser Pro  
 185 190 195  
 Leu Ser Ala Phe Arg Ser Ser Ser Ser Leu Arg Lys Lys Asn Asn  
 200 205 210  
 Ser Gly Glu Lys Ala Leu Pro Pro Trp Arg Ser Ser Asp Lys His  
 215 220 225  
 Pro Thr Asp Ile Ile Arg Phe Asn Tyr Leu Asp Asn Arg Asp Pro  
 230 235 240  
 Met Glu Thr Val Gln Gln Gly Arg Arg Lys Arg Asn Gln Ile Thr  
 245 250 255  
 Pro Asp Phe Ser Arg Gln Ser His Asp Lys Lys Asn Lys Leu Gln  
 260 265 270  
 Asp Arg Thr Arg Leu Arg Lys Ala Gln Ser Met Met Ser Arg Arg  
 275 280 285  
 Asn Pro Phe Pro Leu Cys Pro  
 290

&lt;210&gt; 31

&lt;211&gt; 588

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; misc\_feature

&lt;223&gt; Incyte ID No: 1750781CD1

&lt;400&gt; 31

Met Ser Ser Gly Leu Arg Ala Ala Asp Phe Pro Arg Trp Lys Arg  
 1 5 10 15  
 His Ile Ser Glu Gln Leu Arg Arg Arg Asp Arg Leu Gln Arg Gln  
 20 25 30  
 Ala Phe Glu Glu Ile Ile Leu Gln Tyr Asn Lys Leu Leu Glu Lys  
 35 40 45  
 Ser Asp Leu His Ser Val Leu Ala Gln Lys Leu Gln Ala Glu Lys  
 50 55 60  
 His Asp Val Pro Asn Arg His Glu Ile Ser Pro Gly His Asp Gly  
 65 70 75  
 Thr Trp Asn Asp Asn Gln Leu Gln Glu Met Ala Gln Leu Arg Ile  
 80 85 90  
 Lys His Gln Glu Glu Leu Thr Glu Leu His Lys Lys Arg Gly Glu  
 95 100 105  
 Leu Ala Gln Leu Val Ile Asp Leu Asn Asn Gln Met Gln Arg Lys  
 110 115 120  
 Asp Arg Glu Met Gln Met Asn Glu Ala Lys Ile Ala Glu Cys Leu  
 125 130 135  
 Gln Thr Ile Ser Asp Leu Glu Thr Glu Cys Leu Asp Leu Arg Thr

	140		145		150
Lys Leu Cys Asp	Leu Glu Arg Ala Asn	Gln Thr Leu Lys Asp		Glu	
	155		160		165
Tyr Asp Ala Leu	Gln Ile Thr Phe Thr	Ala Leu Glu Gly Lys		Leu	
	170		175		180
Arg Lys Thr Thr	Glu Glu Asn Gln Glu	Leu Val Thr Arg Trp		Met	
	185		190		195
Ala Glu Lys Ala	Gln Glu Ala Asn Arg	Leu Asn Ala Glu Asn		Glu	
	200		205		210
Lys Asp Ser Arg	Arg Arg Gln Ala Arg	Leu Gln Lys Glu Leu		Ala	
	215		220		225
Glu Ala Ala Lys	Glu Pro Leu Pro Val	Glu Gln Asp Asp Asp		Ile	
	230		235		240
Glu Val Ile Val	Asp Glu Thr Ser Asp	His Thr Glu Glu Thr		Ser	
	245		250		255
Pro Val Arg Ala	Ile Ser Arg Ala Ala	Thr Arg Arg Ser Val		Ser	
	260		265		270
Ser Phe Pro Val	Pro Gln Asp Asn Val	Asp Thr His Pro Gly		Ser	
	275		280		285
Gly Lys Glu Val	Arg Val Pro Ala Thr	Ala Leu Cys Val Phe		Asp	
	290		295		300
Ala His Asp Gly	Glu Val Asn Ala Val	Gln Phe Ser Pro Gly		Ser	
	305		310		315
Arg Leu Leu Ala	Thr Gly Gly Met Asp	Arg Arg Val Lys Leu		Trp	
	320		325		330
Glu Val Phe Gly	Glu Lys Cys Glu Phe	Lys Gly Ser Leu Ser		Gly	
	335		340		345
Ser Asn Ala Gly	Ile Thr Ser Ile Glu	Phe Asp Ser Ala Gly		Ser	
	350		355		360
Tyr Leu Leu Ala	Ala Ser Asn Asp Phe	Ala Ser Arg Ile Trp		Thr	
	365		370		375
Val Asp Asp Tyr	Arg Leu Arg His Thr	Leu Thr Gly His Ser		Gly	
	380		385		390
Lys Val Leu Ser	Ala Lys Phe Leu Leu	Asp Asn Ala Arg Ile		Val	
	395		400		405
Ser Gly Ser His	Asp Arg Thr Leu Lys	Leu Trp Asp Leu Arg		Ser	
	410		415		420
Lys Val Cys Ile	Lys Thr Val Phe Ala	Gly Ser Ser Cys Asn		Asp	
	425		430		435
Ile Val Cys Thr	Glu Gln Cys Val Met	Ser Gly His Phe Asp		Lys	
	440		445		450
Lys Ile Arg Phe	Trp Asp Ile Arg Ser	Glu Ser Ile Val Arg		Glu	
	455		460		465
Met Glu Leu Leu	Gly Lys Ile Thr Ala	Leu Asp Leu Asn Pro		Glu	
	470		475		480
Arg Thr Glu Leu	Leu Ser Cys Ser Arg	Asp Asp Leu Leu Lys		Val	
	485		490		495
Ile Asp Leu Arg	Thr Asn Ala Ile Lys	Gln Thr Phe Ser Ala		Pro	
	500		505		510
Gly Phe Lys Cys	Gly Ser Asp Trp Thr	Arg Val Val Phe Ser		Pro	
	515		520		525
Asp Gly Ser Tyr	Val Ala Ala Gly Ser	Ala Glu Gly Ser Leu		Tyr	
	530		535		540
Ile Trp Ser Val	Leu Thr Gly Lys Val	Glu Lys Val Leu Ser		Lys	
	545		550		555
Gln His Ser Ser	Ser Ile Asn Ala Val	Ala Trp Ser Pro Ser		Gly	
	560		565		570
Ser His Val Val	Ser Val Asp Lys Gly	Cys Lys Ala Val Leu		Trp	
	575		580		585
Ala Gln Tyr					

&lt;210&gt; 32

&lt;211&gt; 326

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; misc\_feature

&lt;223&gt; Incyte ID No: 1821658CD1

&lt;400&gt; 32

```

Met Lys Gln Asp Ala Ser Arg Asn Ala Ala Tyr Thr Val Asp Cys
 1      5      10
Glu Asp Tyr Val His Val Val Glu Phe Asn Pro Phe Glu Asn Gly
 20      25      30
Asp Ser Gly Asn Leu Ile Ala Tyr Gly Gly Asn Asn Tyr Val Val
 35      40      45
Ile Gly Thr Cys Thr Phe Gln Glu Glu Glu Ala Asp Val Glu Gly
 50      55      60
Ile Gln Tyr Lys Thr Leu Arg Thr Phe His His Gly Val Arg Val
 65      70      75
Asp Gly Ile Ala Trp Ser Pro Glu Thr Arg Leu Asp Ser Leu Pro
 80      85      90
Pro Val Ile Lys Phe Cys Thr Ser Ala Ala Asp Met Lys Ile Arg
 95      100     105
Leu Phe Thr Ser Asp Leu Gln Asp Lys Asn Glu Tyr Lys Val Leu
 110     115     120
Glu Gly His Thr Asp Phe Ile Asn Gly Leu Val Phe Asp Pro Lys
 125     130     135
Glu Gly Gln Glu Ile Ala Ser Val Ser Asp Asp His Thr Cys Arg
 140     145     150
Ile Trp Asn Leu Glu Gly Val Gln Thr Ala His Phe Val Leu His
 155     160     165
Ser Pro Gly Met Ser Val Cys Trp His Pro Glu Glu Thr Phe Lys
 170     175     180
Leu Met Val Ala Glu Lys Asn Gly Thr Ile Arg Phe Tyr Asp Leu
 185     190     195
Leu Ala Gln Gln Ala Ile Leu Ser Leu Glu Ser Glu Gln Val Pro
 200     205     210
Leu Met Ser Ala His Trp Cys Leu Lys Asn Thr Phe Lys Val Gly
 215     220     225
Ala Val Ala Gly Asn Asp Trp Leu Ile Trp Asp Ile Thr Arg Ser
 230     235     240
Ser Tyr Pro Gln Asn Lys Arg Pro Val His Met Asp Arg Ala Cys
 245     250     255
Leu Phe Arg Trp Ser Thr Ile Ser Glu Asn Leu Phe Ala Thr Thr
 260     265     270
Gly Tyr Pro Gly Lys Met Ala Ser Gln Phe Gln Ile His His Leu
 275     280     285
Gly His Pro Gln Pro Ile Leu Met Gly Ser Val Ala Val Gly Ser
 290     295     300
Gly Leu Ser Trp His Arg Thr Leu Pro Leu Cys Val Ile Gly Gly
 305     310     315
Asp His Lys Leu Leu Phe Trp Val Thr Glu Val
 320     325

```

&lt;210&gt; 33

&lt;211&gt; 453

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; misc\_feature

&lt;223&gt; Incyte ID No: 1872574CD1

&lt;400&gt; 33

```

Met Ala Arg Lys Val Val Ser Arg Lys Arg Lys Ala Pro Ala Ser

```

1	5	10	15
Pro Gly Ala Gly Ser	Asp Ala Gln Gly	Pro Gln Phe Gly Trp	Asp
20	25	30	
His Ser Leu His Lys	Arg Lys Arg Leu	Pro Pro Val Lys Arg	Ser
35	40	45	
Leu Val Tyr Tyr Leu	Lys Asn Arg Glu	Val Arg Leu Gln Asn	Glu
50	55	60	
Thr Ser Tyr Ser Arg	Val Leu His Gly	Tyr Ala Ala Gln Gln	Leu
65	70	75	
Pro Ser Leu Leu Lys	Glu Arg Glu Phe	His Leu Gly Thr Leu	Asn
80	85	90	
Lys Val Phe Ala Ser	Gln Trp Leu Asn	His Arg Gln Val Val	Cys
95	100	105	
Gly Thr Lys Cys Asn	Thr Leu Phe Val	Val Asp Val Gln Thr	Ser
110	115	120	
Gln Ile Thr Lys Ile	Pro Ile Leu Lys	Asp Arg Glu Pro Gly	Gly
125	130	135	
Val Thr Gln Gln Gly	Cys Gly Ile His	Ala Ile Glu Leu Asn	Pro
140	145	150	
Ser Arg Thr Leu Leu	Ala Thr Gly Gly	Asp Asn Pro Asn Ser	Leu
155	160	165	
Ala Ile Tyr Arg Leu	Pro Thr Leu Asp	Pro Val Cys Val Gly	Asp
170	175	180	
Asp Gly His Lys Asp	Trp Ile Phe Ser	Ile Ala Trp Ile Ser	Asp
185	190	195	
Thr Met Ala Val Ser	Gly Ser Arg Asp	Gly Ser Met Gly Leu	Trp
200	205	210	
Glu Val Thr Asp Asp	Val Leu Thr Lys	Ser Asp Ala Arg His	Asn
215	220	225	
Val Ser Arg Val Pro	Val Tyr Ala His	Ile Thr His Lys Ala	Leu
230	235	240	
Lys Asp Ile Pro Lys	Glu Asp Thr Asn	Pro Asp Asn Cys Lys	Val
245	250	255	
Arg Ala Leu Ala Phe	Asn Asn Lys Asn	Lys Glu Leu Gly Ala	Val
260	265	270	
Ser Leu Asp Gly Tyr	Phe His Leu Trp	Lys Ala Glu Asn Thr	Leu
275	280	285	
Ser Lys Leu Leu Ser	Thr Lys Leu Pro	Tyr Cys Arg Glu Asn	Val
290	295	300	
Cys Leu Ala Tyr Gly	Ser Glu Trp Ser	Val Tyr Ala Val Gly	Ser
305	310	315	
Gln Ala His Val Ser	Phe Leu Asp Pro	Arg Gln Pro Ser Tyr	Asn
320	325	330	
Val Lys Ser Val Cys	Ser Arg Glu Arg	Gly Ser Gly Ile Arg	Ser
335	340	345	
Val Ser Phe Tyr Glu	His Ile Ile Thr	Val Gly Thr Gly Gln	Gly
350	355	360	
Ser Leu Leu Phe Tyr	Asp Ile Arg Ala	Gln Arg Phe Leu Glu	Glu
365	370	375	
Arg Leu Ser Ala Cys	Tyr Gly Ser Lys	Pro Arg Leu Ala Gly	Glu
380	385	390	
Asn Leu Lys Leu Thr	Gly Lys Gly Trp	Leu Asn His Asp	Glu
395	400	405	
Thr Trp Arg Asn Tyr	Phe Ser Asp Ile	Asp Phe Phe Pro Asn	Ala
410	415	420	
Val Tyr Thr His Cys	Tyr Asp Ser Ser	Gly Thr Lys Leu Phe	Val
425	430	435	
Ala Gly Gly Pro Leu	Pro Ser Gly Leu	His Gly Asn Tyr Ala	Gly
440	445	450	

Leu Trp Ser

&lt;210&gt; 34

&lt;211&gt; 161

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<220>  
<221> misc_feature  
<223> Incyte ID No: 2590967CD1
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<210> 35
<211> 684
<212> PRT
<213> Homo sapiens
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<220>  
<221> misc_feature  
<223> Incyte ID No: 2824491CD1
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<400>	35															
Met	Ala	Arg	His	Arg	Asn	Val	Arg	Gly	Tyr	Asn	Tyr	Asp	Glu	Asp		
1				5					10					15		
Phe	Glu	Asp	Asp	Asp	Leu	Tyr	Gly	Gln	Ser	Val	Glu	Asp	Asp	Tyr		
				20					25					30		
Cys	Ile	Ser	Pro	Ser	Thr	Ala	Ala	Gln	Phe	Ile	Tyr	Ser	Arg	Arg		
				35					40					45		
Asp	Lys	Pro	Ser	Val	Glu	Pro	Val	Glu	Glu	Tyr	Asp	Tyr	Glu	Asp		
				50					55					60		
Leu	Lys	Glu	Ser	Ser	Asn	Ser	Val	Ser	Asn	His	Gln	Leu	Ser	Gly		
				65					70					75		
Phe	Asp	Gln	Ala	Arg	Leu	Tyr	Ser	Cys	Leu	Asp	His	Met	Arg	Glu		
				80					85					90		
Val	Leu	Gly	Asp	Ala	Val	Pro	Asp	Glu	Ile	Leu	Ile	Glu	Ala	Val		
				95					100					105		
Leu	Lys	Asn	Lys	Phe	Asp	Val	Gln	Lys	Ala	Leu	Ser	Gly	Val	Leu		
				110					115					120		
Glu	Gln	Asp	Arg	Val	Gln	Ser	Leu	Lys	Asp	Lys	Asn	Glu	Ala	Thr		
				125					130					135		
Val	Ser	Thr	Gly	Lys	Ile	Ala	Lys	Gly	Lys	Pro	Val	Asp	Ser	Gln		
				140					145					150		
Thr	Ser	Arg	Ser	Glu	Ser	Glu	Ile	Val	Pro	Lys	Val	Ala	Lys	Met		
				155					160					165		
Thr	Val	Ser	Gly	Lys	Lys	Gln	Thr	Met	Gly	Phe	Glu	Val	Pro	Gly		

				170					175					180
Val	Ser	Ser	Glu	Glu	Asn	Gly	His	Ser	Phe	His	Thr	Pro	Gln	Lys
				185					190					195
Gly	Pro	Pro	Ile	Glu	Asp	Ala	Ile	Ala	Ser	Ser	Asp	Val	Leu	Glu
				200					205					210
Thr	Ala	Ser	Lys	Ser	Ala	Asn	Pro	Pro	His	Thr	Ile	Gln	Ala	Ser
				215					220					225
Glu	Glu	Gln	Ser	Ser	Thr	Pro	Ala	Pro	Val	Lys	Lys	Ser	Gly	Lys
				230					235					240
Leu	Arg	Gln	Gln	Ile	Asp	Val	Lys	Ala	Glu	Leu	Glu	Lys	Arg	Gln
				245					250					255
Gly	Gly	Lys	Gln	Leu	Leu	Asn	Leu	Val	Val	Ile	Gly	His	Val	Asp
				260					265					270
Ala	Gly	Lys	Ser	Thr	Leu	Met	Gly	His	Met	Leu	Tyr	Leu	Leu	Gly
				275					280					285
Asn	Ile	Asn	Lys	Arg	Thr	Met	His	Lys	Tyr	Glu	Gln	Glu	Ser	Lys
				290					295					300
Lys	Ala	Gly	Lys	Ala	Ser	Phe	Ala	Tyr	Ala	Trp	Val	Leu	Asp	Glu
				305					310					315
Thr	Gly	Glu	Glu	Arg	Glu	Arg	Gly	Val	Thr	Met	Asp	Val	Gly	Met
				320					325					330
Thr	Lys	Phe	Glu	Thr	Thr	Thr	Lys	Val	Ile	Thr	Leu	Met	Asp	Ala
				335					340					345
Pro	Gly	His	Lys	Asp	Phe	Ile	Pro	Asn	Met	Ile	Thr	Gly	Ala	Ala
				350					355					360
Gln	Ala	Asp	Val	Ala	Val	Leu	Val	Val	Asp	Ala	Ser	Arg	Gly	Glu
				365					370					375
Phe	Glu	Ala	Gly	Phe	Glu	Thr	Gly	Gly	Gln	Thr	Arg	Glu	His	Gly
				380					385					390
Leu	Leu	Val	Arg	Ser	Leu	Gly	Val	Thr	Gln	Leu	Ala	Val	Ala	Val
				395					400					405
Asn	Lys	Met	Asp	Gln	Val	Asn	Trp	Gln	Gln	Glu	Arg	Phe	Gln	Glu
				410					415					420
Ile	Thr	Gly	Lys	Leu	Gly	His	Phe	Leu	Lys	Gln	Ala	Gly	Phe	Lys
				425					430					435
Glu	Ser	Asp	Val	Gly	Phe	Ile	Pro	Thr	Ser	Gly	Leu	Ser	Gly	Glu
				440					445					450
Asn	Leu	Ile	Thr	Arg	Ser	Gln	Ser	Ser	Glu	Leu	Thr	Lys	Trp	Tyr
				455					460					465
Lys	Gly	Leu	Cys	Leu	Leu	Glu	Gln	Ile	Asp	Ser	Phe	Lys	Pro	Pro
				470					475					480
Gln	Arg	Ser	Ile	Asp	Lys	Pro	Phe	Arg	Leu	Cys	Val	Ser	Asp	Val
				485					490					495
Phe	Lys	Asp	Gln	Gly	Ser	Gly	Phe	Cys	Ile	Thr	Gly	Lys	Ile	Glu
				500					505					510
Ala	Gly	Tyr	Ile	Gln	Thr	Gly	Asp	Arg	Leu	Leu	Ala	Met	Pro	Pro
				515					520					525
Asn	Glu	Thr	Cys	Thr	Val	Lys	Gly	Ile	Thr	Leu	His	Asp	Glu	Pro
				530					535					540
Val	Asp	Trp	Ala	Ala	Ala	Gly	Asp	His	Val	Ser	Leu	Thr	Leu	Val
				545					550					555
Gly	Met	Asp	Ile	Ile	Lys	Ile	Asn	Val	Gly	Cys	Ile	Phe	Cys	Gly
				560					565					570
Pro	Lys	Val	Pro	Ile	Lys	Ala	Cys	Thr	Arg	Phe	Arg	Ala	Arg	Ile
				575					580					585
Leu	Ile	Phe	Asn	Ile	Glu	Ile	Pro	Ile	Thr	Lys	Gly	Phe	Pro	Val
				590					595					600
Leu	Leu	His	Tyr	Gln	Thr	Val	Ser	Glu	Pro	Ala	Val	Ile	Lys	Arg
				605					610					615
Leu	Ile	Ser	Val	Leu	Asn	Lys	Ser	Thr	Gly	Glu	Val	Thr	Lys	Lys
				620					625					630
Lys	Pro	Lys	Phe	Leu	Thr	Lys	Gly	Gln	Asn	Ala	Leu	Val	Glu	Leu
				635					640					645

Gln Thr Gln Arg Pro Ile Ala Leu Glu Leu Tyr Lys Asp Phe Lys  
 650 655 660  
 Glu Leu Gly Arg Phe Met Leu Arg Tyr Gly Gly Ser Thr Ile Ala  
 665 670 675  
 Ala Gly Val Val Thr Glu Ile Lys Glu  
 680

&lt;210&gt; 36

&lt;211&gt; 366

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; misc\_feature

&lt;223&gt; Incyte ID No: 2825460CD1

&lt;400&gt; 36

Met Ala Ala Ala Ala Arg Trp Asn His Val Trp Val Gly Thr  
 1 5 10 15  
 Glu Thr Gly Ile Leu Lys Gly Val Asn Leu Gln Arg Lys Gln Ala  
 20 25 30  
 Ala Asn Phe Thr Ala Gly Gly Gln Pro Arg Arg Glu Glu Ala Val  
 35 40 45  
 Ser Ala Leu Cys Trp Gly Thr Gly Gly Thr Gln Met Leu Val  
 50 55 60  
 Gly Cys Ala Asp Arg Thr Val Lys His Phe Ser Thr Glu Asp Gly  
 65 70 75  
 Ile Phe Gln Gly Gln Arg His Cys Pro Gly Gly Glu Gly Met Phe  
 80 85 90  
 Arg Gly Leu Ala Gln Ala Asp Gly Thr Leu Ile Thr Cys Val Asp  
 95 100 105  
 Ser Gly Ile Leu Arg Val Trp His Asp Lys Asp Lys Asp Thr Ser  
 110 115 120  
 Ser Asp Pro Leu Leu Glu Leu Arg Val Gly Pro Gly Val Cys Arg  
 125 130 135  
 Met Arg Gln Asp Pro Ala His Pro His Val Ala Thr Gly Gly  
 140 145 150  
 Lys Glu Asn Ala Leu Lys Ile Trp Asp Leu Gln Gly Ser Glu Glu  
 155 160 165  
 Pro Val Phe Arg Ala Lys Asn Val Arg Asn Asp Trp Leu Asp Leu  
 170 175 180  
 Arg Val Pro Ile Trp Asp Gln Asp Ile Gln Phe Leu Pro Gly Ser  
 185 190 195  
 Gln Lys Leu Val Thr Cys Thr Gly Tyr His Gln Val Arg Val Tyr  
 200 205 210  
 Asp Pro Ala Ser Pro Gln Arg Arg Pro Val Leu Glu Thr Thr Tyr  
 215 220 225  
 Gly Glu Tyr Pro Leu Thr Ala Met Thr Leu Thr Pro Gly Gly Asn  
 230 235 240  
 Ser Val Ile Val Gly Asn Thr His Gly Gln Leu Ala Glu Ile Asp  
 245 250 255  
 Leu Arg Gln Gly Arg Leu Leu Gly Cys Leu Lys Gly Leu Ala Gly  
 260 265 270  
 Ser Val Arg Gly Leu Gln Cys His Pro Ser Lys Pro Leu Leu Ala  
 275 280 285  
 Ser Cys Gly Leu Asp Arg Val Leu Arg Ile His Arg Ile Gln Asn  
 290 295 300  
 Pro Arg Gly Leu Glu His Lys Asp Glu Pro Gln Glu Pro Gln Glu  
 305 310 315  
 Pro Asn Lys Val Pro Leu Glu Asp Thr Glu Thr Asp Glu Leu Trp  
 320 325 330  
 Ala Ser Leu Glu Ala Ala Ala Lys Arg Lys Leu Ser Gly Leu Glu  
 335 340 345  
 Gln Pro Gln Gly Ala Leu Gln Thr Arg Arg Arg Lys Lys Lys Arg



350  
 Pro Gly Ser Thr Ser Pro  
 365  
 <210> 37  
 <211> 339  
 <212> PRT  
 <213> Homo sapiens  
  
 <220>  
 <221> misc\_feature  
 <223> Incyte ID No: 2871116CD1  
  
 <400> 37  
 Met Ala Thr Glu Ile Gly Ser Pro Pro Arg Phe Phe His Met Pro  
 1 5 10 15  
 Arg Phe Gln His Gln Ala Pro Arg Gln Leu Phe Tyr Lys Arg Pro  
 20 25 30  
 Asp Phe Ala Gln Gln Gln Ala Met Gln Gln Leu Thr Phe Asp Gly  
 35 40 45  
 Lys Arg Met Arg Lys Ala Val Asn Arg Lys Thr Ile Asp Tyr Asn  
 50 55 60  
 Pro Ser Val Ile Lys Tyr Leu Glu Asn Arg Ile Trp Gln Arg Asp  
 65 70 75  
 Gln Arg Asp Met Arg Ala Ile Gln Pro Asp Ala Gly Tyr Tyr Asn  
 80 85 90  
 Asp Leu Val Pro Pro Ile Gly Met Leu Asn Asn Pro Met Asn Ala  
 95 100 105  
 Val Thr Thr Lys Phe Val Arg Thr Ser Thr Asn Lys Val Lys Cys  
 110 115 120  
 Pro Val Phe Val Val Arg Leu Gln Glu Glu Phe Glu Ser Leu Ser  
 125 130 135  
 Val Leu Lys Ser Trp Thr Pro Glu Gly Arg Arg Leu Val Thr Gly  
 140 145 150  
 Ala Ser Ser Gly Glu Phe Thr Leu Trp Asn Gly Leu Thr Phe Asn  
 155 160 165  
 Phe Glu Thr Ile Leu Gln Ala His Asp Ser Pro Val Arg Ala Met  
 170 175 180  
 Thr Trp Ser His Asn Asp Met Trp Met Leu Thr Ala Asp His Gly  
 185 190 195  
 Gly Tyr Val Lys Tyr Trp Gln Ser Asn Met Asn Asn Val Lys Met  
 200 205 210  
 Phe Gln Ala His Lys Glu Ala Ile Arg Glu Ala Arg Phe Ile His  
 215 220 225  
 Asn Ile Pro Phe Ser Val Val Pro Ile Val Met Val Lys Leu Phe  
 230 235 240  
 Ser Lys Cys Ile Leu Gly Ala Glu Met His Gly Leu Cys Gln Phe  
 245 250 255  
 Leu Gly Asn Phe Leu His Pro Ile Asn Thr Ile Phe Phe Phe Val  
 260 265 270  
 Phe Thr His Ser Pro Phe Cys Trp His Leu Ser Glu Val Val Leu  
 275 280 285  
 Ser Arg Tyr Gln Pro Leu Gln Tyr Val Arg Asp Val Leu Ser Ala  
 290 295 300  
 Ala Phe Cys Thr Gly Phe Leu Phe Ser Phe Met Ile Asn Asn Val  
 305 310 315  
 Tyr Thr Leu Phe Leu Phe Ile Ile Tyr Cys Val Arg Gln Glu Tyr  
 320 325 330  
 Phe Ile Pro Asn Lys Glu Phe Ser Leu  
 335  
 <210> 38  
 <211> 213  
 <212> PRT  
 <213> Homo sapiens

<400>	39														
Met	Glu	Leu	Val	Ala	Gly	Cys	Tyr	Glu	Gln	Val	Leu	Phe	Gly	Phe	
1				5					10					15	
Ala	Val	His	Pro	Glu	Pro	Glu	Ala	Cys	Gly	Asp	His	Glu	Gln	Gln	
				20					25					30	
Trp	Thr	Leu	Val	Ala	Asp	Phe	Thr	His	His	Ala	His	Thr	Ala	Ser	
				35					40					45	
Leu	Ser	Ala	Val	Ala	Val	Asn	Ser	Arg	Phe	Val	Val	Thr	Gly	Ser	
				50					55					60	
Lys	Asp	Glu	Thr	Ile	His	Ile	Tyr	Asp	Met	Lys	Lys	Lys	Ile	Glu	
				65					70					75	
His	Gly	Ala	Leu	Val	His	His	Ser	Gly	Thr	Ile	Thr	Cys	Leu	Thr	
				80					85					90	
Phe	Tyr	Gly	Asn	Arg	His	Leu	Ile	Ser	Gly	Ala	Glu	Asp	Gly	Leu	
				95					100					105	
Ile	Cys	Ile	Trp	Asp	Ala	Lys	Lys	Trp	Glu	Ser	Leu	Thr	Ser	Ile	
				110					115					120	
Lys	Ala	His	Lys	Gly	Gln	Val	Thr	Phe	Leu	Ser	Ile	His	Pro	Ser	
				125					130					135	

Gly Lys Leu Ala Leu Ser Val Gly Thr Asp Lys Thr Leu Arg Thr  
 140 145 150  
 Trp Asn Leu Val Glu Gly Arg Ser Ala Phe Ile Lys Asn Ile Lys  
 155 160 165  
 Gln Asn Ala His Ile Val Glu Trp Ser Pro Arg Gly Glu Gln Tyr  
 170 175 180  
 Val Val Ile Ile Gln Asn Lys Ile Asp Ile Tyr Gln Leu Asp Thr  
 185 190 195  
 Ala Ser Ile Ser Gly Thr Ile Thr Asn Glu Lys Arg Ile Ser Ser  
 200 205 210  
 Val Lys Phe Leu Ser Glu Ser Val Leu Ala Val Ala Gly Asp Glu  
 215 220 225  
 Glu Val Ile Arg Phe Phe Asp Cys Asp Ser Leu Val Cys Leu Cys  
 230 235 240  
 Glu Phe Lys Ala His Glu Asn Arg Val Lys Asp Met Phe Ser Phe  
 245 250 255  
 Glu Ile Pro Glu His His Val Ile Val Ser Ala Ser Ser Asp Gly  
 260 265 270  
 Phe Ile Lys Met Trp Lys Leu Lys Gln Asp Lys Lys Val Pro Pro  
 275 280 285  
 Ser Leu Leu Cys Glu Ile Asn Thr Asn Ala Arg Leu Thr Cys Leu  
 290 295 300  
 Gly Val Trp Leu Asp Lys Val Ala Asp Met Lys Glu Ser Leu Pro  
 305 310 315  
 Pro Ala Ala Glu Pro Ser Pro Val Ser Lys Glu Gln Ser Lys Ile  
 320 325 330  
 Gly Lys Lys Glu Pro Gly Asp Thr Val His Lys Glu Glu Lys Arg  
 335 340 345  
 Ser Lys Pro Asn Thr Lys Lys Arg Gly Leu Thr Gly Asp Ser Lys  
 350 355 360  
 Lys Ala Thr Lys Glu Ser Gly Leu Ile Ser Thr Lys Lys Arg Lys  
 365 370 375  
 Met Val Glu Met Leu Glu Lys Lys Arg Lys Lys Lys Lys Ile Lys  
 380 385 390  
 Thr Met Gln

&lt;210&gt; 40

&lt;211&gt; 399

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; misc\_feature

&lt;223&gt; Incyte ID No: 4881515CD1

&lt;400&gt; 40

Met Ser Leu Gln Tyr Gly Ala Glu Glu Thr Pro Leu Ala Gly Ser  
 1 5 10 15  
 Tyr Gly Ala Ala Asp Ser Phe Pro Lys Asp Phe Gly Tyr Gly Val  
 20 25 30  
 Glu Glu Glu Glu Glu Glu Ala Ala Ala Gly Gly Gly Val Gly  
 35 40 45  
 Ala Gly Ala Gly Gly Gly Cys Gly Pro Gly Gly Ala Asp Ser Ser  
 50 55 60  
 Lys Pro Arg Ile Leu Leu Met Gly Leu Arg Arg Ser Gly Lys Ser  
 65 70 75  
 Ser Ile Gln Lys Val Val Phe His Lys Met Ser Pro Asn Glu Thr  
 80 85 90  
 Leu Phe Leu Glu Ser Thr Asn Lys Ile Tyr Lys Asp Asp Ile Ser  
 95 100 105  
 Asn Ser Ser Phe Val Asn Phe Gln Ile Trp Asp Phe Pro Gly Gln  
 110 115 120  
 Met Asp Phe Phe Asp Pro Thr Phe Asp Tyr Glu Met Ile Phe Arg

	125		130		135
Gly Thr Gly Ala	Leu Ile Tyr Val Ile	Asp Ala Gln Asp Asp	Tyr		
	140		145		150
Met Glu Ala Leu	Thr Arg Leu His Ile	Thr Val Ser Lys Ala	Tyr		
	155		160		165
Lys Val Asn Pro	Asp Met Asn Phe Glu	Val Phe Ile His Lys	Val		
	170		175		180
Asp Gly Leu Ser	Asp Asp His Lys Ile	Glu Thr Gln Arg Asp	Ile		
	185		190		195
His Gln Arg Ala	Asn Asp Asp Leu Ala	Asp Ala Gly Leu Glu	Lys		
	200		205		210
Leu His Leu Ser	Phe Tyr Leu Thr Ser	Ile Tyr Asp His Ser	Ile		
	215		220		225
Phe Glu Ala Phe	Ser Lys Val Val Gln	Lys Leu Ile Pro Gln	Leu		
	230		235		240
Pro Thr Leu Glu	Asn Leu Leu Asn Ile	Phe Ile Ser Asn Ser	Gly		
	245		250		255
Ile Glu Lys Ala	Phe Leu Phe Asp Val	Val Ser Lys Ile Tyr	Ile		
	260		265		270
Ala Thr Asp Ser	Ser Pro Val Asp Met	Gln Ser Tyr Glu Leu	Cys		
	275		280		285
Cys Asp Met Ile	Asp Val Val Ile Asp	Val Ser Cys Ile Tyr	Gly		
	290		295		300
Leu Lys Glu Asp	Gly Ser Gly Ser Ala	Tyr Asp Lys Glu Ser	Met		
	305		310		315
Ala Ile Ile Lys	Leu Asn Asn Thr Thr	Val Leu Tyr Leu Lys	Glu		
	320		325		330
Val Thr Lys Phe	Leu Ala Leu Val Cys	Ile Leu Arg Glu Glu	Ser		
	335		340		345
Phe Glu Arg Lys	Gly Leu Ile Asp Tyr	Asn Phe His Cys Phe	Arg		
	350		355		360
Lys Ala Ile His	Glu Val Phe Glu Val	Gly Val Thr Ser His	Arg		
	365		370		375
Ser Cys Gly His	Gln Thr Ser Ala Ser	Ser Leu Lys Ala Leu	Thr		
	380		385		390
His Asn Gly Thr	Pro Arg Asn Ala Ile				
	395				

&lt;210&gt; 41

&lt;211&gt; 412

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; misc\_feature

&lt;223&gt; Incyte ID No: 5324681CD1

&lt;400&gt; 41

Met Ala Gly Ser Val	Gly Leu Ala Leu Cys	Gly Gln Thr Leu Val
1	5	10
Val Arg Gly Gly Ser	Arg Phe Leu Ala Thr	Ser Ile Ala Ser Ser
	20	25
Asp Asp Asp Ser Leu	Phe Ile Tyr Asp Cys	Ser Ala Ala Glu Lys
	35	40
Lys Ser Gln Glu Asn	Lys Gly Glu Asp Ala	Pro Leu Asp Gln Gly
	50	55
Ser Gly Ala Ile Leu	Ala Ser Thr Phe Ser	Lys Ser Gly Ser Tyr
	65	70
Phe Ala Leu Thr Asp	Asp Ser Lys Arg Leu	Ile Leu Phe Arg Thr
	80	85
Lys Pro Trp Gln Cys	Leu Ser Val Arg Thr	Val Ala Arg Arg Cys
	95	100
Thr Ala Leu Thr Phe	Ile Ala Ser Glu Glu	Lys Val Leu Val Ala
	110	115
		120

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Asp Lys Ser Gly Asp Val Tyr Ser Phe Ser Val Leu Glu Pro His
125 130 135
Gly Cys Gly Arg Leu Glu Leu Gly His Leu Ser Met Leu Leu Asp
140 145 150
Val Ala Val Ser Pro Asp Asp Arg Phe Ile Leu Thr Ala Asp Arg
155 160 165
Asp Glu Lys Ile Arg Val Ser Trp Ala Ala Ala Pro His Ser Ile
170 175 180
Glu Ser Phe Cys Leu Gly His Thr Glu Phe Val Ser Arg Ile Ser
185 190 195
Val Val Pro Thr Gln Pro Gly Leu Leu Leu Ser Ser Ser Gly Asp
200 205 210
Gly Thr Leu Arg Leu Trp Glu Tyr Arg Ser Gly Arg Gln Leu His
215 220 225
Cys Cys His Leu Ala Ser Leu Gln Glu Leu Val Asp Pro Gln Ala
230 235 240
Pro Gln Lys Phe Ala Ala Ser Arg Ile Ala Phe Trp Cys Gln Glu
245 250 255
Asn Cys Val Ala Leu Leu Cys Asp Gly Thr Pro Val Val Tyr Ile
260 265 270
Phe Gln Leu Asp Ala Arg Arg Gln Gln Leu Val Tyr Arg Gln Gln
275 280 285
Leu Ala Phe Gln His Gln Val Trp Asp Val Ala Phe Glu Glu Thr
290 295 300
Gln Gly Leu Trp Val Leu Gln Asp Cys Gln Glu Ala Pro Leu Val
305 310 315
Leu Tyr Arg Pro Val Gly Asp Gln Trp Gln Ser Val Pro Glu Ser
320 325 330
Thr Val Leu Lys Lys Val Ser Gly Val Leu Arg Gly Asn Trp Ala
335 340 345
Met Leu Glu Gly Ser Ala Gly Ala Asp Ala Ser Phe Ser Ser Leu
350 355 360
Tyr Lys Ala Thr Phe Asp Asn Val Thr Ser Tyr Leu Lys Lys Lys
365 370 375
Glu Glu Arg Leu Gln Gln Gln Leu Glu Lys Lys Gln Arg Arg Arg
380 385 390
Ser Pro Pro Pro Gly Pro Asp Gly His Ala Lys Lys Met Arg Pro
395 400 405
Gly Glu Ala Thr Leu Ser Cys
410

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&lt;210&gt; 42

&lt;211&gt; 163

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; misc\_feature

&lt;223&gt; Incyte ID No: 5387651CD1

&lt;400&gt; 42

```

Met Asp Ala Leu Glu Gly Glu Ser Phe Ala Leu Ser Phe Ser Ser
1 5 10 15
Ala Ser Asp Ala Glu Phe Asp Ala Val Val Gly Tyr Leu Glu Asp
20 25 30
Ile Ile Met Asp Asp Glu Phe Gln Leu Leu Gln Arg Asn Phe Met
35 40 45
Asp Lys Tyr Tyr Leu Glu Phe Glu Asp Thr Glu Glu Asn Lys Leu
50 55 60
Ile Tyr Thr Pro Ile Phe Asn Glu Tyr Ile Ser Leu Val Glu Lys
65 70 75
Tyr Ile Glu Glu Gln Leu Leu Gln Arg Ile Pro Glu Phe Asn Met
80 85 90
Ala Ala Phe Thr Thr Thr Leu Gln His His Lys Asp Glu Val Ala

```

	95		100		105
Gly Asp Ile Phe	Asp Met Leu Leu Thr	Phe Thr Asp Phe Leu	Ala		
	110		115		120
Phe Lys Glu Met	Phe Leu Asp Tyr Arg	Ala Glu Lys Glu Gly	Arg		
	125		130		135
Gly Leu Asp Leu	Ser Ser Gly Leu Val	Val Thr Ser Leu Cys	Lys		
	140		145		150
Ser Ser Ser Leu	Pro Ala Ser Gln Asn	Asn Leu Arg His			
	155		160		

&lt;210&gt; 43

&lt;211&gt; 514

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; misc\_feature

&lt;223&gt; Incyte ID No: 5595679CD1

&lt;400&gt; 43

Met Gln Glu Ser Gly	Cys Arg Leu Glu His	Pro Ser Ala Thr Lys	
1	5	10	15
Phe Arg Asn His Val	Met Glu Gly Asp Trp	Asp Lys Ala Glu Asn	
	20	25	30
Asp Leu Asn Glu Leu	Lys Pro Leu Val His	Ser Pro His Ala Ile	
	35	40	45
Val Val Arg Gly Ala	Leu Glu Ile Ser Gln	Thr Leu Leu Gly Ile	
	50	55	60
Ile Val Arg Met Lys	Phe Leu Leu Leu Gln	Gln Lys Tyr Leu Glu	
	65	70	75
Tyr Leu Glu Asp Gly	Lys Val Leu Glu Ala	Leu Gln Val Leu Arg	
	80	85	90
Cys Glu Leu Thr Pro	Leu Lys Tyr Asn Thr	Glu Arg Ile His Val	
	95	100	105
Leu Ser Gly Tyr Leu	Met Cys Ser His Ala	Glu Asp Leu Arg Ala	
	110	115	120
Lys Ala Glu Trp Glu	Gly Lys Gly Thr Ala	Ser Arg Ser Lys Leu	
	125	130	135
Leu Asp Lys Leu Gln	Thr Tyr Leu Pro Pro	Ser Val Met Leu Pro	
	140	145	150
Pro Arg Arg Leu Gln	Thr Leu Leu Arg Gln	Ala Val Glu Leu Gln	
	155	160	165
Arg Asp Arg Cys Leu	Tyr His Asn Thr Lys	Leu Asp Asn Asn Leu	
	170	175	180
Asp Ser Val Ser Leu	Leu Ile Asp His Val	Cys Ser Arg Arg Gln	
	185	190	195
Phe Pro Cys Tyr Thr	Gln Gln Ile Leu Thr	Glu His Cys Asn Glu	
	200	205	210
Val Trp Phe Cys Lys	Phe Ser Asn Asp Gly	Thr Lys Leu Ala Thr	
	215	220	225
Gly Ser Lys Asp Thr	Thr Val Ile Ile Trp	Gln Val Asp Pro Asp	
	230	235	240
Thr His Leu Leu Lys	Leu Leu Lys Thr Leu	Glu Gly His Ala Tyr	
	245	250	255
Gly Val Ser Tyr Ile	Ala Trp Ser Pro Asp	Asp Asn Tyr Leu Val	
	260	265	270
Ala Cys Gly Pro Asp	Asp Cys Ser Glu Leu	Trp Leu Trp Asn Val	
	275	280	285
Gln Thr Gly Glu Leu	Arg Thr Lys Met Ser	Gln Ser His Glu Asp	
	290	295	300
Ser Leu Thr Ser Val	Ala Trp Asn Pro Asp	Gly Lys Arg Phe Val	
	305	310	315
Thr Gly Gly Gln Arg	Gly Gln Phe Tyr Gln	Cys Asp Leu Asp Gly	
	320	325	330

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Asn Leu Leu Asp Ser Trp Glu Gly Val Arg Val Gln Cys Leu Trp
335 340 345
Cys Leu Ser Asp Gly Lys Thr Val Leu Ala Ser Asp Thr His Gln
350 355 360
Arg Ile Arg Gly Tyr Asn Phe Glu Asp Leu Thr Asp Arg Asn Ile
365 370 375
Val Gln Glu Asp His Pro Ile Met Ser Phe Thr Ile Ser Lys Asn
380 385 390
Gly Arg Leu Ala Leu Leu Asn Val Ala Thr Gln Gly Val His Leu
395 400 405
Trp Asp Leu Gln Asp Arg Val Leu Val Arg Lys Tyr Gln Gly Val
410 415 420
Thr Gln Gly Phe Tyr Thr Ile His Ser Cys Phe Gly Gly His Asn
425 430 435
Glu Asp Phe Ile Ala Ser Gly Ser Glu Asp His Lys Val Tyr Ile
440 445 450
Trp His Lys Arg Ser Glu Leu Pro Ile Ala Glu Leu Thr Gly His
455 460 465
Thr Arg Thr Val Asn Cys Val Ser Trp Asn Pro Gln Ile Pro Ser
470 475 480
Met Met Ala Ser Ala Ser Asp Asp Gly Thr Val Arg Ile Trp Gly
485 490 495
Pro Ala Pro Phe Ile Asp His Gln Asn Ile Glu Glu Glu Cys Ser
500 505 510
Ser Met Asp Ser

```

&lt;210&gt; 44

&lt;211&gt; 67

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; misc\_feature

&lt;223&gt; Incyte ID No: 5782457CD1

&lt;400&gt; 44

```

Met Glu Glu Trp Asp Val Pro Gln Met Lys Lys Glu Val Glu Ser
1 5 10 15
Leu Lys Tyr Gln Leu Ala Phe Gln Arg Glu Met Ala Ser Lys Thr
20 25 30
Ile Pro Glu Leu Leu Lys Trp Ile Glu Asp Gly Ile Pro Lys Asp
35 40 45
Pro Phe Leu Asn Pro Asp Leu Met Lys Asn Asn Pro Trp Val Glu
50 55 60
Lys Gly Lys Cys Thr Ile Leu
65

```

&lt;210&gt; 45

&lt;211&gt; 315

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; misc\_feature

&lt;223&gt; Incyte ID No: 760677CD1

&lt;400&gt; 45

```

Met Ala Phe Pro Glu Pro Lys Pro Arg Pro Pro Glu Leu Pro Gln
1 5 10 15
Lys Arg Leu Lys Thr Leu Asp Cys Gly Gln Gly Ala Val Arg Ala
20 25 30
Val Arg Phe Asn Val Asp Gly Asn Tyr Cys Leu Thr Cys Gly Ser
35 40 45
Asp Lys Thr Leu Lys Leu Trp Asn Pro Leu Arg Gly Thr Leu Leu

```

	50		55		60
Arg Thr Tyr Ser Gly His Gly Tyr Glu Val Leu Asp Ala Ala Gly					
	65		70		75
Ser Phe Asp Asn Ser Ser Leu Cys Ser Gly Gly Gly Asp Lys Ala					
	80		85		90
Val Val Leu Trp Asn Val Ala Ser Gly Gln Val Val Arg Lys Phe					
	95		100		105
Arg Gly His Ala Gly Lys Val Asn Thr Val Gln Phe Ser Glu Glu					
	110		115		120
Ala Thr Val Ile Leu Ser Gly Ser Ile Asp Ser Ser Ile Arg Cys					
	125		130		135
Trp Asp Cys Arg Ser Arg Arg Pro Glu Pro Val Gln Thr Leu Asp					
	140		145		150
Glu Ala Arg Asp Gly Val Ser Ser Val Lys Val Ser Asp His Glu					
	155		160		165
Ile Leu Ala Gly Ser Val Asp Gly Arg Val Arg Arg Tyr Asp Leu					
	170		175		180
Arg Met Gly Gln Leu Phe Ser Asp Tyr Val Gly Ser Pro Ile Thr					
	185		190		195
Cys Thr Cys Phe Ser Arg Asp Gly Gln Cys Thr Leu Val Ser Ser					
	200		205		210
Leu Asp Ser Thr Leu Arg Leu Leu Asp Lys Asp Thr Gly Glu Leu					
	215		220		225
Leu Gly Glu Tyr Lys Gly His Lys Asn Gln Glu Tyr Lys Leu Asp					
	230		235		240
Cys Cys Leu Ser Glu Arg Asp Thr His Val Val Ser Cys Ser Glu					
	245		250		255
Asp Gly Lys Val Phe Phe Trp Asp Leu Val Glu Gly Ala Leu Ala					
	260		265		270
Leu Ala Leu Pro Val Gly Ser Gly Val Val Gln Ser Leu Asp Tyr					
	275		280		285
His Pro Thr Glu Pro Cys Leu Leu Thr Ala Met Gly Gly Ser Val					
	290		295		300
Gln Cys Trp Arg Glu Glu Ala Tyr Glu Ala Glu Asp Gly Ala Gly					
	305		310		315

&lt;210&gt; 46

&lt;211&gt; 504

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; misc\_feature

&lt;223&gt; Incyte ID No: 1348567CD1

&lt;400&gt; 46

Met Ser Leu Ile Cys Ser Ile Ser Asn Glu Val Pro Glu His Pro					
1	5		10		15
Cys Val Ser Pro Val Ser Asn His Val Tyr Glu Arg Arg Leu Ile					
	20		25		30
Glu Lys Tyr Ile Ala Glu Asn Gly Thr Asp Pro Ile Asn Asn Gln					
	35		40		45
Pro Leu Ser Glu Glu Gln Leu Ile Asp Ile Lys Val Ala His Pro					
	50		55		60
Ile Arg Pro Lys Pro Pro Ser Ala Thr Ser Ile Pro Ala Ile Leu					
	65		70		75
Lys Ala Leu Gln Asp Glu Trp Asp Ala Val Met Pro His Ser Phe					
	80		85		90
Thr Leu Arg Gln Gln Leu Gln Thr Thr Arg Gln Glu Leu Ser His					
	95		100		105
Ala Leu Tyr Gln His Asp Ala Ala Cys Arg Val Ile Ala Arg Leu					
	110		115		120
Thr Lys Glu Val Thr Ala Ala Arg Glu Ala Leu Ala Thr Leu Lys					



Pro Gln Ala Gly	125	130	135
Leu Ile Val Pro Gln	140	145	150
Pro Ser Val Val Gly	155	160	165
Ala Gly Glu Pro Met	170	175	180
Val Gly Met Thr Pro	185	190	195
Glu Glu Leu Val Lys	200	205	210
Ala Ser His Val Gly	215	220	225
Ala Leu Asp Leu Cys	230	235	240
Gly Ala Asp Lys Asn	245	250	255
Ile Leu Ala Thr Leu	260	265	270
Val Phe His Pro Ser	275	280	285
Ala Thr Ile Arg Ile	290	295	300
Val Val Arg Ala His	305	310	315
Ala Thr Gly Asp Tyr	320	325	330
Ala Phe Ser Asp Ile	335	340	345
Asp Glu Thr Ser Gly	350	355	360
Asp Gly Leu Ile Phe	365	370	375
Ile Trp Asp Leu Lys	380	385	390
His Ser Gly Pro Ile	395	400	405
Tyr Leu Ala Thr Ala	410	415	420
Leu Arg Lys Leu Lys	425	430	435
Phe Glu Val Lys Ser	440	445	450
Ala Leu Gly Gly Thr	455	460	465
Thr Glu Ile Leu His	470	475	480
Val Ala Phe Gly His	485	490	495
Asp Arg Ser Leu Lys	500		

&lt;210&gt; 47

&lt;211&gt; 522

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; misc\_feature

&lt;223&gt; Incyte ID No: 1751354CD1

&lt;400&gt; 47

Met	Ala	Phe	Leu	Asp	Asn	Pro	Thr	Ile	Ile	Leu	Ala	His	Ile	Arg
1				5					10				15	

Gln	Ser	His	Val	Thr	Ser	Asp	Asp	Thr	Gly	Met	Cys	Glu	Met	Val
				20					25					30
Leu	Ile	Asp	His	Asp	Val	Asp	Leu	Glu	Lys	Ile	His	Pro	Pro	Ser
				35					40					45
Met	Pro	Gly	Asp	Ser	Gly	Ser	Glu	Ile	Gln	Gly	Ser	Asn	Gly	Glu
				50					55					60
Thr	Gln	Gly	Tyr	Val	Tyr	Ala	Gln	Ser	Val	Asp	Ile	Thr	Ser	Ser
				65					70					75
Trp	Asp	Phe	Gly	Ile	Arg	Arg	Arg	Ser	Asn	Thr	Ala	Gln	Arg	Leu
				80					85					90
Glu	Arg	Leu	Arg	Lys	Glu	Arg	Gln	Asn	Gln	Ile	Lys	Cys	Lys	Asn
				95					100					105
Ile	Gln	Trp	Lys	Glu	Arg	Asn	Ser	Lys	Gln	Ser	Ala	Gln	Glu	Leu
				110					115					120
Lys	Ser	Leu	Phe	Glu	Lys	Lys	Ser	Leu	Lys	Glu	Lys	Pro	Pro	Ile
				125					130					135
Ser	Gly	Lys	Gln	Ser	Ile	Leu	Ser	Val	Arg	Leu	Glu	Gln	Cys	Pro
				140					145					150
Leu	Gln	Leu	Asn	Asn	Pro	Phe	Asn	Glu	Tyr	Ser	Lys	Phe	Asp	Gly
				155					160					165
Lys	Gly	His	Val	Gly	Thr	Thr	Ala	Thr	Lys	Lys	Ile	Asp	Val	Tyr
				170					175					180
Leu	Pro	Leu	His	Ser	Ser	Gln	Asp	Arg	Leu	Leu	Pro	Met	Thr	Val
				185					190					195
Val	Thr	Met	Ala	Ser	Ala	Arg	Val	Gln	Asp	Leu	Ile	Gly	Leu	Ile
				200					205					210
Cys	Trp	Gln	Tyr	Thr	Ser	Glu	Gly	Arg	Glu	Pro	Lys	Leu	Asn	Asp
				215					220					225
Asn	Val	Ser	Ala	Tyr	Cys	Leu	His	Ile	Ala	Glu	Asp	Asp	Gly	Glu
				230					235					240
Val	Asp	Thr	Asp	Phe	Pro	Pro	Leu	Asp	Ser	Asn	Glu	Pro	Ile	His
				245					250					255
Lys	Phe	Gly	Phe	Ser	Thr	Leu	Ala	Leu	Val	Glu	Lys	Tyr	Ser	Ser
				260					265					270
Pro	Gly	Leu	Thr	Ser	Lys	Glu	Ser	Leu	Phe	Val	Arg	Ile	Asn	Ala
				275					280					285
Ala	His	Gly	Phe	Ser	Leu	Ile	Gln	Val	Asp	Asn	Thr	Lys	Val	Thr
				290					295					300
Met	Lys	Glu	Ile	Leu	Leu	Lys	Ala	Val	Lys	Arg	Arg	Lys	Gly	Ser
				305					310					315
Gln	Lys	Val	Ser	Gly	Pro	Gln	Tyr	Arg	Leu	Glu	Lys	Gln	Ser	Glu
				320					325					330
Pro	Asn	Val	Ala	Val	Asp	Leu	Asp	Ser	Thr	Leu	Glu	Ser	Gln	Ser
				335					340					345
Ala	Trp	Glu	Phe	Cys	Leu	Val	Arg	Glu	Asn	Ser	Ser	Arg	Ala	Asp
				350					355					360
Gly	Val	Phe	Glu	Glu	Asp	Ser	Gln	Ile	Asp	Ile	Ala	Thr	Val	Gln
				365					370					375
Asp	Met	Leu	Ser	Ser	His	His	Tyr	Lys	Ser	Phe	Lys	Val	Ser	Met
				380					385					390
Ile	His	Arg	Leu	Arg	Phe	Thr	Thr	Asp	Val	Gln	Leu	Gly	Ile	Ser
				395					400					405
Gly	Asp	Lys	Val	Glu	Ile	Asp	Pro	Val	Thr	Asn	Gln	Lys	Ala	Ser
				410					415					420
Thr	Lys	Phe	Trp	Ile	Lys	Gln	Lys	Pro	Ile	Ser	Ile	Asp	Ser	Asp
				425					430					435
Leu	Leu	Cys	Ala	Cys	Asp	Leu	Ala	Glu	Glu	Lys	Ser	Pro	Ser	His
				440					445					450
Ala	Ile	Phe	Lys	Leu	Thr	Tyr	Leu	Ser	Asn	His	Asp	Tyr	Lys	His
				455					460					465
Leu	Tyr	Phe	Glu	Ser	Asp	Ala	Ala	Thr	Val	Asn	Glu	Ile	Val	Leu
				470					475					480
Lys	Val	Asn	Tyr	Ile	Leu	Glu	Ser	Arg	Ala	Ser	Thr	Ala	Arg	Ala

	485	490	495
Asp Tyr Phe Ala Gln Lys Gln Arg Lys	Leu Asn Arg Arg Thr Ser		
	500	505	510
Phe Ser Phe Gln Lys Glu Lys Lys Ser	Gly Gln Gln		
	515	520	

<210> 48  
 <211> 316  
 <212> PRT  
 <213> Homo sapiens

<220>  
 <221> misc\_feature  
 <223> Incyte ID No: 1976780CD1

<400> 48

Met Ala Ser Lys Asp Lys Ser Ser Lys Lys Asn Val Phe Glu Leu	
1	15
Lys Thr Arg Gln Gly Thr Glu Leu Leu Ile Gln Ser Asp Asn Asp	
	30
Thr Val Ile Asn Asp Trp Phe Lys Val Leu Ser Ser Thr Ile Asn	
	45
Asn Gln Ala Val Glu Thr Asp Glu Gly Ile Glu Glu Glu Ile Pro	
	60
Asp Ser Pro Gly Ile Glu Lys His Asp Lys Glu Lys Glu Gln Lys	
	75
Asp Pro Lys Lys Leu Arg Ser Phe Lys Val Ser Ser Ile Asp Ser	
	90
Ser Glu Gln Lys Lys Thr Lys Lys Asn Leu Lys Lys Phe Leu Thr	
	105
Arg Arg Pro Thr Leu Gln Ala Val Arg Glu Lys Gly Tyr Ile Lys	
	120
Asp Gln Val Phe Gly Ser Asn Leu Ala Asn Leu Cys Gln Arg Glu	
	135
Asn Gly Thr Val Pro Lys Phe Val Lys Leu Cys Ile Glu His Val	
	150
Glu Glu His Gly Leu Asp Ile Asp Gly Ile Tyr Arg Val Ser Gly	
	165
Asn Leu Ala Val Ile Gln Lys Leu Arg Phe Ala Val Asn His Asp	
	180
Glu Lys Leu Asp Leu Asn Asp Ser Lys Trp Glu Asp Ile His Val	
	195
Ile Thr Gly Ala Leu Lys Met Phe Phe Arg Glu Leu Pro Glu Pro	
	210
Leu Phe Thr Phe Asn His Phe Asn Asp Phe Val Asn Ala Ile Lys	
	225
Gln Glu Pro Arg Gln Arg Val Ala Ala Val Lys Asp Leu Ile Arg	
	240
Gln Leu Pro Lys Pro Asn Gln Asp Thr Met Gln Ile Leu Phe Arg	
	255
His Leu Arg Arg Val Ile Glu Asn Gly Glu Lys Asn Arg Met Thr	
	270
Tyr Gln Ser Ile Ala Ile Val Phe Gly Pro Thr Leu Leu Lys Pro	
	285
Glu Lys Glu Thr Gly Asn Ile Ala Val His Thr Val Tyr Gln Asn	
	300
Gln Ile Val Glu Leu Ile Leu Leu Glu Leu Ser Ser Ile Phe Gly	
	315

Arg

<210> 49  
 <211> 387  
 <212> PRT  
 <213> Homo sapiens

&lt;220&gt;

&lt;221&gt; misc\_feature

&lt;223&gt; Incyte ID No: 2048234CD1

&lt;400&gt; 49

Met	Val	His	Cys	Ser	Cys	Val	Leu	Phe	Arg	Lys	Tyr	Gly	Asn	Phe
1				5					10					15
Ile	Asp	Lys	Leu	Arg	Leu	Phe	Thr	Arg	Gly	Gly	Ser	Gly	Gly	Met
				20					25					30
Gly	Tyr	Pro	Arg	Leu	Gly	Gly	Glu	Gly	Gly	Lys	Gly	Gly	Asp	Val
				35					40					45
Trp	Val	Val	Ala	Gln	Asn	Arg	Met	Thr	Leu	Lys	Gln	Leu	Lys	Asp
				50					55					60
Arg	Tyr	Pro	Arg	Lys	Arg	Phe	Val	Ala	Gly	Val	Gly	Ala	Asn	Ser
				65					70					75
Lys	Ile	Ser	Ala	Leu	Lys	Gly	Ser	Lys	Gly	Lys	Asp	Trp	Glu	Ile
				80					85					90
Pro	Val	Pro	Val	Gly	Ile	Ser	Val	Thr	Asp	Glu	Asn	Gly	Lys	Ile
				95					100					105
Ile	Gly	Glu	Leu	Ser	Lys	Glu	Asn	Asp	Arg	Ile	Leu	Val	Ala	Gln
				110					115					120
Gly	Gly	Leu	Gly	Gly	Lys	Leu	Leu	Thr	Asn	Phe	Leu	Pro	Leu	Lys
				125					130					135
Gly	Gln	Lys	Arg	Ile	Ile	His	Leu	Asp	Leu	Lys	Leu	Ile	Ala	Asp
				140					145					150
Val	Gly	Leu	Val	Gly	Phe	Pro	Asn	Ala	Gly	Lys	Ser	Ser	Leu	Leu
				155					160					165
Ser	Cys	Val	Ser	His	Ala	Lys	Pro	Ala	Ile	Ala	Asp	Tyr	Ala	Phe
				170					175					180
Thr	Thr	Leu	Lys	Leu	Lys	Leu	Gly	Lys	Ile	Met	Tyr	Ser	Asp	Phe
				185					190					195
Lys	Gln	Ile	Ser	Val	Ala	Asp	Leu	Pro	Gly	Leu	Ile	Glu	Gly	Ala
				200					205					210
His	Met	Asn	Lys	Gly	Met	Gly	His	Lys	Phe	Leu	Lys	His	Ile	Glu
				215					220					225
Arg	Thr	Arg	Gln	Leu	Leu	Phe	Val	Val	Asp	Ile	Ser	Gly	Phe	Gln
				230					235					240
Leu	Ser	Ser	His	Thr	Gln	Tyr	Arg	Thr	Ala	Phe	Glu	Thr	Ile	Ile
				245					250					255
Leu	Leu	Thr	Lys	Glu	Leu	Glu	Leu	Tyr	Lys	Glu	Glu	Leu	Gln	Thr
				260					265					270
Lys	Pro	Ala	Leu	Leu	Ala	Val	Asn	Lys	Met	Asp	Leu	Pro	Asp	Ala
				275					280					285
Gln	Asp	Lys	Phe	His	Glu	Leu	Met	Ser	Gln	Leu	Gln	Asn	Pro	Lys
				290					295					300
Asp	Phe	Leu	His	Leu	Phe	Glu	Lys	Asn	Met	Ile	Pro	Glu	Arg	Thr
				305					310					315
Val	Glu	Phe	Gln	His	Ile	Ile	Pro	Ile	Ser	Ala	Val	Thr	Gly	Glu
				320					325					330
Gly	Ile	Glu	Glu	Leu	Lys	Asn	Cys	Ile	Arg	Lys	Ser	Leu	Asp	Glu
				335					340					345
Gln	Ala	Asn	Gln	Glu	Asn	Asp	Ala	Leu	His	Lys	Lys	Gln	Leu	Leu
				350					355					360
Asn	Leu	Trp	Ile	Ser	Asp	Thr	Met	Ser	Ser	Thr	Glu	Pro	Pro	Ser
				365					370					375
Lys	His	Ala	Val	Thr	Thr	Ser	Lys	Met	Asp	Ile	Ile			
				380					385					

&lt;210&gt; 50

&lt;211&gt; 334

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; misc\_feature

&lt;223&gt; Incyte ID No: 2111754CD1

&lt;400&gt; 50

```

Met Pro Ser Gly Pro Arg Ala Ala Leu Arg Trp Ala Ser Pro Ser
 1          5          10          15
Gln Leu Val Ser Tyr His Val Leu Arg Asn Gly Ile Tyr Ala Cys
 20          25          30
Tyr Pro His Ser Leu Arg Pro Arg Thr Pro Leu Leu Cys Ala Ser
 35          40          45
Arg Asn Ile Lys Pro Arg Arg Ser Glu Leu Leu Gly Cys Pro Val
 50          55          60
Gly Cys Arg Gly Ser Leu Ser Glu Gln Arg Ile Cys Leu Leu Gly
 65          70          75
Cys Leu Val Arg Ala Ser Glu Lys Gly Val Ser Cys Cys Gln Leu
 80          85          90
Ser Val Gly Glu Leu Val His Val Ser Pro Leu Arg Ile Pro Thr
 95          100          105
Met Gly Asn Ala Ser Phe Gly Ser Lys Glu Gln Lys Leu Leu Lys
110          115          120
Arg Leu Arg Leu Leu Pro Ala Leu Leu Ile Leu Arg Ala Phe Lys
125          130          135
Pro His Arg Lys Ile Arg Asp Tyr Arg Val Val Val Val Gly Thr
140          145          150
Ala Gly Val Gly Lys Ser Thr Leu Leu His Lys Trp Ala Ser Gly
155          160          165
Asn Phe Arg His Glu Tyr Leu Pro Thr Ile Glu Asn Thr Tyr Cys
170          175          180
Gln Leu Leu Gly Cys Ser His Gly Val Leu Ser Leu His Ile Thr
185          190          195
Asp Ser Lys Ser Gly Asp Gly Asn Arg Ala Leu Gln Arg His Val
200          205          210
Ile Ala Arg Gly His Ala Phe Val Leu Val Tyr Ser Val Thr Lys
215          220          225
Lys Glu Thr Leu Glu Glu Leu Lys Ala Phe Tyr Glu Leu Ile Cys
230          235          240
Lys Ile Lys Gly Asn Asn Leu His Lys Phe Pro Ile Val Leu Val
245          250          255
Gly Asn Lys Ser Asp Asp Thr His Arg Glu Val Ala Leu Asn Asp
260          265          270
Gly Ala Thr Cys Ala Met Glu Trp Asn Cys Ala Phe Met Glu Ile
275          280          285
Ser Ala Lys Thr Asp Val Asn Val Gln Glu Leu Phe His Met Leu
290          295          300
Leu Asn Tyr Lys Lys Lys Pro Thr Thr Gly Leu Gln Glu Pro Glu
305          310          315
Lys Lys Ser Gln Met Pro Asn Thr Thr Glu Lys Leu Leu Asp Lys
320          325          330
Cys Ile Ile Met

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&lt;210&gt; 51

&lt;211&gt; 551

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; misc\_feature

&lt;223&gt; Incyte ID No: 2123286CD1

&lt;400&gt; 51

```

Met Glu Glu Glu Leu Pro Leu Phe Ser Gly Asp Ser Gly Lys Pro
 1          5          10          15
Val Gln Ala Thr Leu Ser Ser Leu Lys Met Leu Asp Val Gly Lys

```

	20		25		30
Trp Pro Ile Phe Ser	Leu Cys Ser Glu	Glu Glu Leu Gln Leu	Ile		
	35		40		45
Arg Gln Ala Cys Val	Phe Gly Ser Ala	Gly Asn Glu Val Leu	Tyr		
	50		55		60
Thr Thr Val Asn Asp	Glu Ile Phe Val	Leu Gly Thr Asn Cys	Cys		
	65		70		75
Gly Cys Leu Gly Leu	Gly Asp Val Gln	Ser Thr Ile Glu Pro	Arg		
	80		85		90
Arg Leu Asp Ser Leu	Asn Gly Lys Lys	Ile Ala Cys Leu Ser	Tyr		
	95		100		105
Gly Ser Gly Pro His	Ile Val Leu Ala	Thr Thr Glu Gly Glu	Val		
	110		115		120
Phe Thr Trp Gly His	Asn Ala Tyr Ser	Gln Leu Gly Asn Gly	Thr		
	125		130		135
Thr Asn His Gly Leu	Val Pro Cys His	Ile Ser Thr Asn Leu	Ser		
	140		145		150
Asn Lys Gln Val Ile	Glu Val Ala Cys	Gly Ser Tyr His Ser	Leu		
	155		160		165
Val Leu Thr Ser Asp	Gly Glu Val Phe	Ala Trp Gly Tyr Asn	Asn		
	170		175		180
Ser Gly Gln Val Gly	Ser Gly Ser Thr	Val Asn Gln Pro Ile	Pro		
	185		190		195
Arg Arg Val Thr Gly	Cys Leu Gln Asn	Lys Val Val Val Thr	Ile		
	200		205		210
Ala Cys Gly Gln Met	Cys Cys Met Ala	Val Val Asp Thr Gly	Glu		
	215		220		225
Val Tyr Val Trp Gly	Tyr Asn Gly Asn	Gly Gln Leu Gly Leu	Gly		
	230		235		240
Asn Ser Gly Asn Gln	Pro Thr Pro Cys	Arg Val Ala Ala Leu	Gln		
	245		250		255
Gly Ile Arg Val Gln	Arg Val Ala Cys	Gly Tyr Ala His Thr	Leu		
	260		265		270
Val Leu Thr Asp Glu	Gly Gln Val Tyr	Ala Trp Gly Ala Asn	Ser		
	275		280		285
Tyr Gly Gln Leu Gly	Thr Gly Asn Lys	Ser Asn Gln Ser Tyr	Pro		
	290		295		300
Thr Pro Val Thr Val	Glu Lys Asp Arg	Ile Ile Glu Ile Ala	Ala		
	305		310		315
Cys His Ser Thr His	Thr Ser Ala Ala	Lys Thr Gln Gly Gly	His		
	320		325		330
Val Tyr Met Trp Gly	Gln Cys Arg Gly	Gln Ser Val Ile Leu	Pro		
	335		340		345
His Leu Thr His Phe	Ser Cys Thr Asp	Asp Val Phe Ala Cys	Phe		
	350		355		360
Ala Thr Pro Ala Val	Thr Trp Arg Leu	Leu Ser Val Glu Pro	Asp		
	365		370		375
Asp His Leu Thr Val	Ala Glu Ser Leu	Lys Arg Glu Phe Asp	Asn		
	380		385		390
Pro Asp Thr Ala Asp	Leu Lys Phe Leu	Val Asp Gly Lys Tyr	Ile		
	395		400		405
Tyr Ala His Lys Val	Leu Leu Lys Ile	Arg Cys Glu His Phe	Arg		
	410		415		420
Ser Ser Leu Glu Asp	Asn Glu Asp Asp	Ile Val Glu Met Ser	Glu		
	425		430		435
Phe Ser Tyr Pro Val	Tyr Arg Ala Phe	Leu Glu Tyr Leu Tyr	Thr		
	440		445		450
Asp Ser Ile Ser Leu	Ser Pro Glu Glu	Ala Val Gly Leu Leu	Asp		
	455		460		465
Leu Ala Thr Phe Tyr	Arg Glu Asn Arg	Leu Lys Lys Leu Cys	Gln		
	470		475		480
Gln Thr Ile Lys Gln	Gly Ile Cys Glu	Glu Asn Ala Ile Ala	Leu		
	485		490		495

Leu Ser Ala Ala Val Lys Tyr Asp Ala Gln Asp Leu Glu Glu Phe  
 500 505 510  
 Cys Phe Arg Phe Cys Ile Asn His Leu Thr Val Val Thr Gln Thr  
 515 520 525  
 Ser Gly Phe Ala Glu Met Asp His Asp Leu Leu Lys Asn Phe Ile  
 530 535 540  
 Ser Lys Ala Ser Arg Val Gly Ala Phe Lys Asn  
 545 550

&lt;210&gt; 52

&lt;211&gt; 308

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; misc\_feature

&lt;223&gt; Incyte ID No: 2477507CD1

&lt;400&gt; 52

Met Ile His Asp Ala Gln Met Asp Tyr Tyr Gly Thr Arg Leu Ala  
 1 5 10 15  
 Thr Cys Ser Ser Asp Arg Ser Val Lys Ile Phe Asp Val Arg Asn  
 20 25 30  
 Gly Gly Gln Ile Leu Ile Ala Asp Leu Arg Gly His Glu Gly Pro  
 35 40 45  
 Val Trp Gln Val Ala Trp Ala His Pro Met Tyr Gly Asn Ile Leu  
 50 55 60  
 Ala Ser Cys Ser Tyr Asp Arg Lys Val Ile Ile Trp Arg Glu Glu  
 65 70 75  
 Asn Gly Thr Trp Glu Lys Ser His Glu His Ala Gly His Asp Ser  
 80 85 90  
 Ser Val Asn Ser Val Cys Trp Ala Pro His Asp Tyr Gly Leu Ile  
 95 100 105  
 Leu Ala Cys Gly Ser Ser Asp Gly Ala Ile Ser Leu Leu Thr Tyr  
 110 115 120  
 Thr Gly Glu Gly Gln Trp Glu Val Lys Lys Ile Asn Asn Ala His  
 125 130 135  
 Thr Ile Gly Cys Asn Ala Val Ser Trp Ala Pro Ala Val Val Pro  
 140 145 150  
 Gly Ser Leu Ile Asp His Pro Ser Gly Gln Lys Pro Asn Tyr Ile  
 155 160 165  
 Lys Arg Phe Ala Ser Gly Gly Cys Asp Asn Leu Ile Lys Leu Trp  
 170 175 180  
 Lys Glu Glu Glu Asp Gly Gln Trp Lys Glu Glu Gln Lys Leu Glu  
 185 190 195  
 Ala His Ser Asp Trp Val Arg Asp Val Ala Trp Ala Pro Ser Ile  
 200 205 210  
 Gly Leu Pro Thr Ser Thr Ile Ala Ser Cys Ser Gln Asp Gly Arg  
 215 220 225  
 Val Phe Ile Trp Thr Cys Asp Asp Ala Ser Ser Asn Thr Trp Ser  
 230 235 240  
 Pro Lys Leu Leu His Lys Phe Asn Asp Val Val Trp His Val Ser  
 245 250 255  
 Trp Ser Ile Thr Ala Asn Ile Leu Ala Val Ser Gly Gly Asp Asn  
 260 265 270  
 Lys Val Thr Leu Trp Lys Glu Ser Val Asp Gly Gln Trp Val Cys  
 275 280 285  
 Ile Ser Asp Val Asn Lys Gly Gln Gly Ser Val Ser Ala Ser Val  
 290 295 300  
 Thr Glu Gly Gln Gln Asn Glu Gln  
 305

&lt;210&gt; 53

&lt;211&gt; 949

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; misc\_feature

&lt;223&gt; Incyte ID No: 2759119CD1

&lt;400&gt; 53

Met	Asp	Ala	Leu	Glu	Asp	Tyr	Val	Trp	Pro	Arg	Ala	Thr	Ser	Glu	
1				5					10					15	
Leu	Ile	Leu	Leu	Pro	Val	Thr	Gly	Leu	Glu	Cys	Val	Gly	Asp	Arg	
				20					25					30	
Leu	Leu	Ala	Gly	Glu	Gly	Pro	Asp	Val	Leu	Val	Tyr	Ser	Leu	Asp	
				35					40					45	
Phe	Gly	Gly	His	Leu	Arg	Met	Ile	Lys	Arg	Val	Gln	Asn	Leu	Leu	
				50					55					60	
Gly	His	Tyr	Leu	Ile	His	Gly	Phe	Arg	Val	Arg	Pro	Glu	Pro	Asn	
				65					70					75	
Gly	Asp	Leu	Asp	Leu	Glu	Ala	Met	Val	Ala	Val	Phe	Gly	Ser	Lys	
				80					85					90	
Gly	Leu	Arg	Val	Val	Lys	Ile	Ser	Trp	Gly	Gln	Gly	His	Phe	Trp	
				95					100					105	
Glu	Leu	Trp	Arg	Ser	Gly	Leu	Trp	Asn	Met	Ser	Asp	Trp	Ile	Trp	
				110					115					120	
Asp	Ala	Arg	Trp	Leu	Glu	Gly	Asn	Ile	Ala	Leu	Ala	Leu	Gly	His	
				125					130					135	
Asn	Ser	Val	Val	Leu	Tyr	Asp	Pro	Val	Val	Gly	Cys	Ile	Leu	Gln	
				140					145					150	
Glu	Val	Pro	Cys	Thr	Asp	Arg	Cys	Thr	Leu	Ser	Ser	Ala	Cys	Leu	
				155					160					165	
Ile	Gly	Asp	Ala	Trp	Lys	Glu	Leu	Thr	Ile	Val	Ala	Gly	Ala	Val	
				170					175					180	
Ser	Asn	Gln	Leu	Leu	Val	Trp	Tyr	Pro	Ala	Thr	Ala	Leu	Ala	Asp	
				185					190					195	
Asn	Lys	Pro	Val	Ala	Pro	Asp	Arg	Arg	Ile	Ser	Gly	His	Val	Gly	
				200					205					210	
Ile	Ile	Phe	Ser	Met	Ser	Tyr	Leu	Glu	Ser	Lys	Gly	Leu	Leu	Ala	
				215					220					225	
Thr	Ala	Ser	Glu	Asp	Arg	Ser	Val	Arg	Ile	Trp	Lys	Val	Gly	Asp	
				230					235					240	
Leu	Arg	Val	Pro	Gly	Gly	Arg	Val	Gln	Asn	Ile	Gly	His	Cys	Phe	
				245					250					255	
Gly	His	Ser	Ala	Arg	Val	Trp	Gln	Val	Lys	Leu	Leu	Glu	Asn	Tyr	
				260					265					270	
Leu	Ile	Ser	Ala	Gly	Glu	Asp	Cys	Val	Cys	Leu	Val	Trp	Ser	His	
				275					280					285	
Glu	Gly	Glu	Ile	Leu	Gln	Ala	Phe	Arg	Gly	His	Gln	Gly	Arg	Gly	
				290					295					300	
Ile	Arg	Ala	Ile	Ala	Ala	His	Glu	Arg	Gln	Ala	Trp	Val	Ile	Thr	
				305					310					315	
Gly	Gly	Asp	Asp	Ser	Gly	Ile	Arg	Leu	Trp	His	Leu	Val	Gly	Arg	
				320					325					330	
Gly	Tyr	Arg	Gly	Leu	Gly	Val	Ser	Ala	Leu	Cys	Phe	Lys	Ser	Arg	
				335					340					345	
Ser	Arg	Pro	Gly	Thr	Leu	Lys	Ala	Val	Thr	Leu	Ala	Gly	Ser	Trp	
				350					355					360	
Arg	Leu	Leu	Ala	Val	Thr	Asp	Thr	Gly	Ala	Leu	Tyr	Leu	Tyr	Asp	
				365					370					375	
Val	Glu	Val	Lys	Cys	Trp	Glu	Gln	Leu	Leu	Glu	Asp	Lys	His	Phe	
				380					385					390	
Gln	Ser	Tyr	Cys	Leu	Leu	Glu	Ala	Ala	Pro	Gly	Pro	Glu	Gly	Phe	
				395					400					405	
Gly	Leu	Cys	Ala	Met	Ala	Asn	Gly	Glu	Gly	Arg	Val	Lys	Val	Val	
				410					415					420	



Pro	Ile	Asn	Thr	Pro	Thr	Ala	Ala	Val	Asp	Gln	Thr	Leu	Phe	Pro
				425					430					435
Gly	Lys	Val	His	Ser	Leu	Ser	Trp	Ala	Leu	Arg	Gly	Tyr	Glu	Glu
				440					445					450
Leu	Leu	Leu	Leu	Ala	Ser	Gly	Pro	Gly	Gly	Val	Val	Ala	Cys	Leu
				455					460					465
Glu	Ile	Ser	Ala	Ala	Pro	Ser	Gly	Lys	Ala	Ile	Phe	Val	Lys	Glu
				470					475					480
Arg	Cys	Arg	Tyr	Leu	Leu	Pro	Pro	Ser	Lys	Gln	Arg	Trp	His	Thr
				485					490					495
Cys	Ser	Ala	Phe	Leu	Pro	Pro	Gly	Asp	Phe	Leu	Val	Cys	Gly	Asp
				500					505					510
Arg	Arg	Gly	Ser	Val	Leu	Leu	Phe	Pro	Ser	Arg	Pro	Gly	Leu	Leu
				515					520					525
Lys	Asp	Pro	Gly	Val	Gly	Gly	Lys	Ala	Arg	Ala	Gly	Ala	Gly	Ala
				530					535					540
Pro	Val	Val	Gly	Ser	Gly	Ser	Ser	Gly	Gly	Gly	Asn	Ala	Phe	Thr
				545					550					555
Gly	Leu	Gly	Pro	Val	Ser	Thr	Leu	Pro	Ser	Leu	His	Gly	Lys	Gln
				560					565					570
Gly	Val	Thr	Ser	Val	Thr	Cys	His	Gly	Gly	Tyr	Val	Tyr	Thr	Ile
				575					580					585
Gly	Arg	Asp	Gly	Ala	Tyr	Tyr	Gln	Leu	Phe	Val	Arg	Asp	Gly	Gln
				590					595					600
Leu	Gln	Pro	Val	Leu	Arg	Gln	Lys	Ser	Cys	Arg	Gly	Met	Asn	Trp
				605					610					615
Leu	Ala	Gly	Leu	Arg	Ile	Val	Pro	Asp	Gly	Ser	Met	Val	Ile	Leu
				620					625					630
Gly	Phe	His	Ala	Asn	Glu	Phe	Val	Val	Trp	Asn	Pro	Arg	Ser	His
				635					640					645
Glu	Lys	Leu	His	Ile	Val	Asn	Cys	Gly	Gly	Gly	His	Arg	Ser	Trp
				650					655					660
Ala	Phe	Ser	Asp	Thr	Glu	Ala	Ala	Met	Ala	Phe	Ala	Tyr	Leu	Lys
				665					670					675
Asp	Gly	Asp	Val	Met	Leu	Tyr	Arg	Ala	Leu	Gly	Gly	Cys	Thr	Arg
				680					685					690
Pro	His	Val	Ile	Leu	Arg	Glu	Gly	Leu	His	Gly	Arg	Glu	Ile	Thr
				695					700					705
Cys	Val	Lys	Arg	Val	Gly	Thr	Ile	Thr	Leu	Gly	Pro	Glu	Tyr	Gly
				710					715					720
Val	Pro	Ser	Phe	Met	Gln	Pro	Asp	Asp	Leu	Glu	Pro	Gly	Ser	Glu
				725					730					735
Gly	Pro	Asp	Leu	Thr	Asp	Ile	Val	Ile	Thr	Cys	Ser	Glu	Asp	Thr
				740					745					750
Thr	Val	Cys	Val	Leu	Ala	Leu	Pro	Thr	Thr	Thr	Gly	Ser	Ala	His
				755					760					765
Ala	Leu	Thr	Ala	Val	Cys	Asn	His	Ile	Ser	Ser	Val	Arg	Ala	Val
				770					775					780
Ala	Val	Trp	Gly	Ile	Gly	Thr	Pro	Gly	Gly	Pro	Gln	Asp	Pro	Gln
				785					790					795
Pro	Gly	Leu	Thr	Ala	His	Val	Val	Ser	Ala	Gly	Gly	Arg	Ala	Glu
				800					805					810
Met	His	Cys	Phe	Ser	Ile	Met	Val	Thr	Pro	Asp	Pro	Ser	Thr	Pro
				815					820					825
Ser	Arg	Leu	Ala	Cys	His	Val	Met	His	Leu	Ser	Ser	His	Arg	Leu
				830					835					840
Asp	Glu	Tyr	Trp	Asp	Arg	Gln	Arg	Asn	Arg	His	Arg	Met	Val	Lys
				845					850					855
Val	Asp	Pro	Glu	Thr	Arg	Tyr	Met	Ser	Leu	Ala	Val	Cys	Glu	Leu
				860					865					870
Asp	Gln	Pro	Gly	Leu	Gly	Pro	Leu	Val	Ala	Ala	Ala	Cys	Ser	Asp
				875					880					885
Gly	Ala	Val	Ser	Ser	Phe	Phe	Cys	Arg	Ile	Leu	Gly	Gly	Phe	Cys

	890		895		900
Ser Ser Leu Leu	Lys Pro Ser Thr Ile	Ser Asp Val Ser Ser	Arg		
	905		910		915
Ser Thr Pro Leu	His Thr Arg His Pro	Thr Arg Gly Gly Gly	Ser		
	920		925		930
Ser Cys Ala Ala	Gln Leu Leu Met Ala	Ala Trp Leu Ser Gly	Ile		
	935		940		945
Ser Pro Pro Cys					

&lt;210&gt; 54

&lt;211&gt; 227

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; misc\_feature

&lt;223&gt; Incyte ID No: 2823818CD1

&lt;400&gt; 54

Met Arg His Glu Ala	Pro Met Gln Met Ala	Ser Ala Gln Asp Ala	
1	5	10	15
Arg Tyr Gly Gln Lys	Asp Ser Ser Asp Gln	Asn Phe Asp Tyr Met	
	20	25	30
Phe Lys Leu Leu Ile	Ile Gly Asn Ser Ser	Val Gly Lys Thr Ser	
	35	40	45
Phe Leu Phe Arg Tyr	Ala Asp Asp Ser Phe	Thr Ser Ala Phe Val	
	50	55	60
Ser Thr Val Gly Ile	Asp Phe Lys Val Lys	Thr Val Phe Lys Asn	
	65	70	75
Val Lys Arg Ile Lys	Leu Gln Ile Trp Asp	Thr Ala Gly Gln Glu	
	80	85	90
Arg Tyr Arg Thr Ile	Thr Thr Ala Tyr Tyr	Arg Gly Ala Met Gly	
	95	100	105
Phe Ile Leu Met Tyr	Asp Ile Thr Asn Glu	Glu Ser Phe Asn Ala	
	110	115	120
Val Gln Asp Trp Ser	Thr Gln Ile Lys Thr	Tyr Ser Trp Asp Asn	
	125	130	135
Ala Gln Val Ile Leu	Val Gly Asn Lys Cys	Asp Met Glu Asp Glu	
	140	145	150
Arg Val Ile Ser Thr	Glu Arg Gly Gln His	Leu Gly Glu Gln Leu	
	155	160	165
Gly Phe Glu Phe Phe	Glu Thr Ser Ala Lys	Asp Asn Ile Asn Val	
	170	175	180
Lys Gln Thr Phe Glu	Arg Leu Val Asp Ile	Ile Cys Asp Lys Met	
	185	190	195
Ser Glu Ser Leu Glu	Thr Asp Pro Ala Ile	Thr Ala Ala Lys Gln	
	200	205	210
Asn Thr Arg Leu Lys	Glu Thr Pro Pro Pro	Pro Gln Pro Asn Cys	
	215	220	225
Ala Cys			

&lt;210&gt; 55

&lt;211&gt; 474

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; misc\_feature

&lt;223&gt; Incyte ID No: 2859730CD1

&lt;400&gt; 55

Met Arg Arg Val Val	Arg Gln Ser Lys Phe	Arg His Val Phe Gly
1	5	10
		15

Gln	Ala	Val	Lys	Asn	Asp	Gln	Cys	Tyr	Asp	Asp	Ile	Arg	Val	Ser	
				20					25					30	
Arg	Val	Thr	Trp	Asp	Ser	Ser	Phe	Cys	Ala	Val	Asn	Pro	Arg	Phe	
				35					40					45	
Val	Ala	Ile	Ile	Ile	Glu	Ala	Ser	Gly	Gly	Gly	Ala	Phe	Leu	Val	
				50					55					60	
Leu	Pro	Leu	Arg	Lys	Thr	Gly	Arg	Ile	Asp	Lys	Ser	Tyr	Pro	Thr	
				65					70					75	
Val	Cys	Gly	His	Thr	Gly	Pro	Val	Leu	Asp	Ile	Asp	Trp	Cys	Pro	
				80					85					90	
His	Asn	Asp	Gln	Val	Ile	Ala	Ser	Gly	Ser	Glu	Asp	Cys	Thr	Val	
				95					100					105	
Met	Val	Trp	Gln	Ile	Pro	Glu	Asn	Gly	Leu	Thr	Leu	Ser	Leu	Thr	
				110					115					120	
Glu	Pro	Val	Val	Ile	Leu	Glu	Gly	His	Ser	Lys	Arg	Val	Gly	Ile	
				125					130					135	
Val	Ala	Trp	His	Pro	Thr	Ala	Arg	Asn	Val	Leu	Leu	Ser	Ala	Gly	
				140					145					150	
Cys	Asp	Asn	Ala	Ile	Ile	Ile	Trp	Asn	Val	Gly	Thr	Gly	Glu	Ala	
				155					160					165	
Leu	Ile	Asn	Leu	Asp	Asp	Met	His	Ser	Asp	Met	Ile	Tyr	Asn	Val	
				170					175					180	
Ser	Trp	Asn	Arg	Asn	Gly	Ser	Leu	Ile	Cys	Thr	Ala	Ser	Lys	Asp	
				185					190					195	
Lys	Lys	Val	Arg	Val	Ile	Asp	Pro	Arg	Lys	Gln	Glu	Ile	Val	Ala	
				200					205					210	
Glu	Lys	Glu	Lys	Ala	His	Glu	Gly	Ala	Arg	Pro	Met	Arg	Ala	Ile	
				215					220					225	
Phe	Leu	Ala	Asp	Gly	Asn	Val	Phe	Thr	Thr	Gly	Phe	Ser	Arg	Met	
				230					235					240	
Ser	Glu	Arg	Gln	Leu	Ala	Leu	Trp	Asn	Pro	Lys	Asn	Met	Gln	Glu	
				245					250					255	
Pro	Ile	Ala	Leu	His	Glu	Met	Asp	Thr	Ser	Asn	Gly	Val	Leu	Leu	
				260					265					270	
Pro	Phe	Tyr	Asp	Pro	Asp	Thr	Ser	Ile	Ile	Tyr	Leu	Cys	Gly	Lys	
				275					280					285	
Gly	Asp	Ser	Ser	Ile	Arg	Tyr	Phe	Glu	Ile	Thr	Asp	Glu	Ser	Pro	
				290					295					300	
Tyr	Val	His	Tyr	Leu	Asn	Thr	Phe	Ser	Ser	Lys	Glu	Pro	Gln	Arg	
				305					310					315	
Gly	Met	Gly	Tyr	Met	Pro	Lys	Arg	Gly	Leu	Asp	Val	Asn	Lys	Cys	
				320					325					330	
Glu	Ile	Ala	Arg	Phe	Phe	Lys	Leu	His	Glu	Arg	Lys	Cys	Glu	Pro	
				335					340					345	
Ile	Ile	Met	Thr	Val	Pro	Arg	Lys	Ser	Asp	Leu	Phe	Gln	Asp	Asp	
				350					355					360	
Leu	Tyr	Pro	Asp	Thr	Ala	Gly	Pro	Glu	Ala	Ala	Leu	Glu	Ala	Glu	
				365					370					375	
Glu	Trp	Phe	Glu	Gly	Lys	Asn	Ala	Asp	Pro	Ile	Leu	Ile	Ser	Leu	
				380					385					390	
Lys	His	Gly	Tyr	Ile	Pro	Gly	Lys	Asn	Arg	Asp	Leu	Lys	Val	Val	
				395					400					405	
Lys	Lys	Asn	Ile	Leu	Asp	Ser	Lys	Pro	Thr	Ala	Asn	Lys	Lys	Cys	
				410					415					420	
Asp	Leu	Ile	Ser	Ile	Pro	Lys	Lys	Thr	Thr	Asp	Thr	Ala	Ser	Val	
				425					430					435	
Gln	Asn	Glu	Ala	Lys	Leu	Asp	Glu	Ile	Leu	Lys	Glu	Ile	Lys	Ser	
				440					445					450	
Ile	Lys	Asp	Thr	Ile	Cys	Asn	Gln	Asp	Glu	Arg	Ile	Ser	Lys	Leu	
				455					460					465	
Glu	Gln	Gln	Met	Ala	Lys	Ile	Ala	Ala							
				470											

&lt;210&gt; 56

<211> 547  
 <212> PRT  
 <213> Homo sapiens

<220>  
 <221> misc\_feature  
 <223> Incyte ID No: 2861155CD1

<400> 56  
 Met Lys Thr Leu Glu Thr Gln Pro Leu Ala Pro Asp Cys Cys Pro  
 1 5 10 15  
 Ser Asp Gln Asp Pro Ala Pro Ala His Pro Ser Pro His Ala Ser  
 20 25 30  
 Pro Met Asn Lys Asn Ala Asp Ser Glu Leu Met Pro Pro Pro Pro  
 35 40 45  
 Glu Arg Gly Asp Pro Pro Arg Leu Ser Pro Asp Pro Val Ala Gly  
 50 55 60  
 Ser Ala Val Ser Gln Glu Leu Arg Glu Gly Asp Pro Val Ser Leu  
 65 70 75  
 Ser Thr Pro Leu Glu Thr Glu Phe Gly Ser Pro Ser Glu Leu Ser  
 80 85 90  
 Pro Arg Ile Glu Glu Gln Glu Leu Ser Glu Asn Thr Ser Leu Pro  
 95 100 105  
 Ala Glu Glu Ala Asn Gly Ser Leu Ser Glu Glu Glu Ala Asn Gly  
 110 115 120  
 Pro Glu Leu Gly Ser Gly Lys Ala Met Glu Asp Thr Ser Gly Glu  
 125 130 135  
 Pro Ala Ala Glu Asp Glu Gly Asp Thr Ala Trp Asn Tyr Ser Phe  
 140 145 150  
 Ser Gln Leu Pro Arg Phe Leu Ser Gly Ser Trp Ser Glu Phe Ser  
 155 160 165  
 Thr Gln Pro Glu Asn Phe Leu Lys Gly Cys Lys Trp Ala Pro Asp  
 170 175 180  
 Gly Ser Cys Ile Leu Thr Asn Ser Ala Asp Asn Ile Leu Arg Ile  
 185 190 195  
 Tyr Asn Leu Pro Pro Glu Leu Tyr His Glu Gly Glu Gln Val Glu  
 200 205 210  
 Tyr Ala Glu Met Val Pro Val Leu Arg Met Val Glu Gly Asp Thr  
 215 220 225  
 Ile Tyr Asp Tyr Cys Trp Tyr Ser Leu Met Ser Ser Ala Gln Pro  
 230 235 240  
 Asp Thr Ser Tyr Val Ala Ser Ser Ser Arg Glu Asn Pro Ile His  
 245 250 255  
 Ile Trp Asp Ala Phe Thr Gly Glu Leu Arg Ala Ser Phe Arg Ala  
 260 265 270  
 Tyr Asn His Leu Asp Glu Leu Thr Ala Ala His Ser Leu Cys Phe  
 275 280 285  
 Ser Pro Asp Gly Ser Gln Leu Phe Cys Gly Phe Asn Arg Thr Val  
 290 295 300  
 Arg Val Phe Ser Thr Ala Arg Pro Gly Arg Asp Cys Glu Val Arg  
 305 310 315  
 Ala Thr Phe Ala Lys Lys Gln Gly Gln Ser Gly Ile Ile Ser Cys  
 320 325 330  
 Ile Ala Phe Ser Pro Ala Gln Pro Leu Tyr Ala Cys Gly Ser Tyr  
 335 340 345  
 Gly Arg Ser Leu Gly Leu Tyr Ala Trp Asp Asp Gly Ser Pro Leu  
 350 355 360  
 Ala Leu Leu Gly Gly His Gln Gly Gly Ile Thr His Leu Cys Phe  
 365 370 375  
 His Pro Asp Gly Asn Arg Phe Phe Ser Gly Ala Arg Lys Asp Ala  
 380 385 390  
 Glu Leu Leu Cys Trp Asp Leu Arg Gln Ser Gly Tyr Pro Leu Trp  
 395 400 405

Ser	Leu	Gly	Arg	Glu	Val	Thr	Thr	Asn	Gln	Arg	Ile	Tyr	Phe	Asp
				410					415					420
Leu	Asp	Pro	Thr	Gly	Gln	Phe	Leu	Val	Ser	Gly	Ser	Thr	Ser	Gly
				425					430					435
Ala	Val	Ser	Val	Trp	Asp	Thr	Asp	Gly	Pro	Gly	Asn	Asp	Gly	Lys
				440					445					450
Pro	Glu	Pro	Val	Leu	Ser	Phe	Leu	Pro	Gln	Lys	Asp	Cys	Thr	Asn
				455					460					465
Gly	Val	Ser	Leu	His	Pro	Ser	Leu	Pro	Leu	Leu	Ala	Thr	Ala	Ser
				470					475					480
Gly	Gln	Arg	Val	Phe	Pro	Glu	Pro	Thr	Glu	Ser	Gly	Asp	Glu	Gly
				485					490					495
Glu	Glu	Leu	Gly	Leu	Pro	Leu	Leu	Ser	Thr	Arg	His	Val	His	Leu
				500					505					510
Glu	Cys	Arg	Leu	Gln	Leu	Trp	Trp	Cys	Gly	Gly	Gly	Pro	Asp	Ser
				515					520					525
Ser	Ile	Pro	Asp	Asp	His	Gln	Gly	Glu	Lys	Gly	Gln	Gly	Gly	Thr
				530					535					540
Gly	Gly	Arg	Ser	Trp	Gly	Ala								
				545										

&lt;210&gt; 57

&lt;211&gt; 686

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; misc\_feature

&lt;223&gt; Incyte ID No: 3002667CD1

&lt;400&gt; 57

Met	Gly	Glu	Phe	Lys	Val	His	Arg	Val	Arg	Phe	Phe	Asn	Tyr	Val
1				5					10					15
Pro	Ser	Gly	Ile	Arg	Cys	Val	Ala	Tyr	Asn	Asn	Gln	Ser	Asn	Arg
				20					25					30
Leu	Ala	Val	Ser	Arg	Thr	Asp	Gly	Thr	Val	Glu	Ile	Tyr	Asn	Leu
				35					40					45
Ser	Ala	Asn	Tyr	Phe	Gln	Glu	Lys	Phe	Phe	Pro	Gly	His	Glu	Ser
				50					55					60
Arg	Ala	Thr	Glu	Ala	Leu	Cys	Trp	Ala	Glu	Gly	Gln	Arg	Leu	Phe
				65					70					75
Ser	Ala	Gly	Leu	Asn	Gly	Glu	Ile	Met	Glu	Tyr	Asp	Leu	Gln	Ala
				80					85					90
Leu	Asn	Ile	Lys	Tyr	Ala	Met	Asp	Ala	Phe	Gly	Gly	Pro	Ile	Trp
				95					100					105
Ser	Met	Ala	Ala	Ser	Pro	Ser	Gly	Ser	Gln	Leu	Leu	Val	Gly	Cys
				110					115					120
Glu	Asp	Gly	Ser	Val	Lys	Leu	Phe	Gln	Ile	Thr	Pro	Asp	Lys	Ile
				125					130					135
Gln	Phe	Glu	Arg	Asn	Phe	Asp	Arg	Gln	Lys	Ser	Arg	Ile	Leu	Ser
				140					145					150
Leu	Ser	Trp	His	Pro	Ser	Gly	Thr	His	Ile	Ala	Ala	Gly	Ser	Ile
				155					160					165
Asp	Tyr	Ile	Ser	Val	Phe	Asp	Val	Lys	Ser	Gly	Ser	Ala	Val	His
				170					175					180
Lys	Met	Ile	Val	Asp	Arg	Gln	Tyr	Met	Gly	Val	Ser	Lys	Arg	Lys
				185					190					195
Cys	Ile	Val	Trp	Gly	Val	Ala	Phe	Leu	Ser	Asp	Gly	Thr	Ile	Ile
				200					205					210
Ser	Val	Asp	Ser	Ala	Gly	Lys	Val	Gln	Phe	Trp	Asp	Ser	Ala	Thr
				215					220					225
Gly	Thr	Leu	Val	Lys	Ser	His	Leu	Ile	Ala	Asn	Ala	Asp	Val	Gln
				230					235					240
Ser	Ile	Ala	Val	Ala	Asp	Gln	Glu	Asp	Ser	Phe	Val	Val	Gly	Thr

Ala Glu Gly Thr	245	Leu Val Pro Val Thr Ser	250	255
	260	Thr Lys Pro Phe Gln His	265	270
Asn Ser Ser Glu	275	His Ser Pro Thr Ala Leu	280	285
His Thr His Asp	290	Val Phe Arg Pro Leu Met	295	300
	305	Ala Ala Leu Arg Lys Ile	310	315
Ile Ser Gly Gly	320	Cys Ser Lys Lys Arg Gln	325	330
Glu Lys Val Glu	335	Leu Glu Leu Trp Arg Leu	340	345
Thr Phe Pro His	350	Gly Asp Thr Leu Pro Leu	355	360
	365	Leu Lys Thr Lys Gly Pro	370	375
Leu Leu Leu Phe	380	Pro Cys Gly Ser Trp Ile	385	390
Gly Ser Thr Val	395	Leu Tyr Arg Leu Asn Tyr	400	405
Ser Lys Asn Ala	410	Val Ser Lys Met Pro Ala	415	420
	425	Phe Ser Glu Asp Ser Thr	430	435
Glu Asn Ile Ile	440	Ala Leu His Ile Val Gln	445	450
Ala Tyr Ser Thr	455	His Ala Phe Gln Pro Gln	460	465
	470	Leu Ala Val Ser Pro Asp	475	480
Glu His Asp Asn	485	Ser Ala Gly Val His Val	490	495
Phe Leu Arg Ser	500	Cys Thr Val Pro Ala Tyr	505	510
Lys Leu Phe Val	515	Ala Pro Asn Thr Asn Asn	520	525
	530	Val Phe Glu Tyr Ser Ile	535	540
Leu Ser Gly Gly	545	Arg Thr Val Gln Lys Gln	550	555
	560	Asp Thr Pro Ile Thr His	565	570
Ser Gly Thr Val	575	His Ile Leu Leu His Asp	580	585
	590	Ser Leu Pro Leu Pro Asn	595	600
Gly Asn Trp Leu	605	Pro Pro Thr Asn Glu Ser	610	615
Tyr Asn Val Lys	620	Ala Phe Lys Ile Ser Lys	625	630
	635	Leu Leu Asp Glu Arg Thr	640	645
Asn Phe Pro Val	650	Asp Ile Ile Ala Gln Leu	655	660
Leu Val Ile Ala	665	Gly Thr	670	675
Pro Asp Lys Gln	680		685	

&lt;210&gt; 58

&lt;211&gt; 93

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; misc\_feature

&lt;223&gt; Incyte ID No: 3043734CD1

&lt;400&gt; 58

Met	Thr	Ser	Lys	Arg	Lys	Pro	Cys	Gln	Thr	Gln	Leu	Arg	Arg	Ser
1				5					10					15
Ile	Ser	Glu	Gln	Leu	Arg	Asp	Ser	Thr	Ala	Arg	Ala	Trp	Asp	Leu
				20					25					30
Leu	Trp	Lys	Asn	Val	Arg	Glu	Arg	Arg	Leu	Ala	Glu	Ile	Glu	Ala
				35					40					45
Lys	Glu	Ala	Cys	Asp	Trp	Leu	Arg	Ala	Ala	Gly	Phe	Pro	Gln	Tyr
				50					55					60
Ala	Gln	Leu	Tyr	Glu	Asp	Ser	Gln	Phe	Pro	Ile	Asn	Ile	Val	Ala
				65					70					75
Val	Lys	Asn	Asp	His	Asp	Phe	Leu	Glu	Lys	Asp	Leu	Val	Glu	Pro
				80					85					90

Leu Cys Arg

&lt;210&gt; 59

&lt;211&gt; 521

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; misc\_feature

&lt;223&gt; Incyte ID No: 3294893CD1

&lt;400&gt; 59

Met	Arg	Arg	Gly	His	Gly	Gln	Arg	Arg	Gly	Gln	Glu	Ala	Ile	Leu
1				5					10					15
Glu	Ala	His	Asn	Ser	Lys	Leu	Pro	Gly	Ser	Ile	Gln	His	Val	Tyr
				20					25					30
Gly	Ala	Gln	His	Pro	Pro	Phe	Asp	Pro	Leu	Leu	His	Gly	Thr	Leu
				35					40					45
Leu	Arg	Ser	Thr	Ala	Lys	Met	Pro	Thr	Thr	Pro	Val	Lys	Ala	Lys
				50					55					60
Arg	Val	Ser	Thr	Phe	Gln	Glu	Phe	Glu	Ser	Asn	Thr	Ser	Asp	Ala
				65					70					75
Trp	Asp	Ala	Gly	Glu	Asp	Asp	Asp	Glu	Leu	Leu	Ala	Met	Ala	Ala
				80					85					90
Glu	Ser	Leu	Asn	Ser	Glu	Val	Val	Met	Glu	Thr	Ala	Asn	Arg	Val
				95					100					105
Leu	Arg	Asn	His	Ser	Gln	Arg	Gln	Gly	Arg	Pro	Thr	Leu	Gln	Glu
				110					115					120
Gly	Pro	Gly	Leu	Gln	Gln	Lys	Pro	Arg	Pro	Glu	Ala	Glu	Pro	Pro
				125					130					135
Ser	Pro	Pro	Ser	Gly	Asp	Leu	Arg	Leu	Val	Lys	Ser	Val	Ser	Glu
				140					145					150
Ser	His	Thr	Ser	Cys	Pro	Ala	Glu	Ser	Ala	Ser	Asp	Ala	Ala	Pro
				155					160					165
Leu	Gln	Arg	Ser	Gln	Ser	Leu	Pro	His	Ser	Ala	Thr	Val	Thr	Leu
				170					175					180
Gly	Gly	Thr	Ser	Asp	Pro	Ser	Thr	Leu	Ser	Ser	Ser	Ala	Leu	Ser
				185					190					195
Glu	Arg	Glu	Ala	Ser	Arg	Leu	Asp	Lys	Phe	Lys	Gln	Leu	Leu	Ala
				200					205					210
Gly	Pro	Asn	Thr	Asp	Leu	Glu	Glu	Leu	Arg	Arg	Leu	Ser	Trp	Ser
				215					220					225
Gly	Ile	Pro	Lys	Pro	Val	Arg	Pro	Met	Thr	Trp	Lys	Leu	Leu	Ser
				230					235					240
Gly	Tyr	Leu	Pro	Ala	Asn	Val	Asp	Arg	Arg	Pro	Ala	Thr	Leu	Gln
				245					250					255

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Arg Lys Gln Lys Glu Tyr Phe Ala Phe Ile Glu His Tyr Tyr Asp
260 265 270
Ser Arg Asn Asp Glu Val His Gln Asp Thr Tyr Arg Gln Ile His
275 280 285
Ile Asp Ile Pro Arg Met Ser Pro Glu Ala Leu Ile Leu Gln Pro
290 295 300
Lys Val Thr Glu Ile Phe Glu Arg Ile Leu Phe Ile Trp Ala Ile
305 310 315
Arg His Pro Ala Ser Gly Tyr Val Gln Gly Ile Asn Asp Leu Val
320 325 330
Thr Pro Phe Phe Val Val Phe Ile Cys Glu Tyr Ile Glu Ala Glu
335 340 345
Glu Val Asp Thr Val Asp Val Ser Gly Val Pro Ala Glu Val Leu
350 355 360
Cys Asn Ile Glu Ala Asp Thr Tyr Trp Cys Met Ser Lys Leu Leu
365 370 375
Asp Gly Ile Gln Asp Asn Tyr Thr Phe Ala Gln Pro Gly Ile Gln
380 385 390
Met Lys Val Lys Met Leu Glu Glu Leu Val Ser Arg Ile Asp Glu
395 400 405
Gln Val His Arg His Leu Asp Gln His Glu Val Arg Tyr Leu Gln
410 415 420
Phe Ala Phe Arg Trp Met Asn Asn Leu Leu Met Arg Glu Val Pro
425 430 435
Leu Arg Cys Thr Ile Arg Leu Trp Asp Thr Tyr Gln Ser Glu Pro
440 445 450
Asp Gly Phe Ser His Phe His Leu Tyr Val Cys Ala Ala Phe Leu
455 460 465
Val Arg Trp Arg Lys Glu Ile Leu Glu Glu Lys Asp Phe Gln Glu
470 475 480
Leu Leu Leu Phe Leu Gln Asn Leu Pro Thr Ala His Trp Asp Asp
485 490 495
Glu Asp Ile Ser Leu Leu Leu Ala Glu Ala Tyr Arg Leu Lys Phe
500 505 510
Ala Phe Ala Asp Ala Pro Asn His Tyr Lys Lys
515 520

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&lt;210&gt; 60

&lt;211&gt; 751

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; misc\_feature

&lt;223&gt; Incyte ID No: 3349052CD1

&lt;400&gt; 60

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Met Arg Leu Leu Gly Ala Ala Ala Val Ala Ala Leu Gly Arg Gly
1 5 10 15
Arg Ala Pro Ala Ser Leu Gly Trp Gln Arg Lys Gln Val Asn Trp
20 25 30
Lys Ala Cys Arg Trp Ser Ser Ser Gly Val Ile Pro Asn Glu Lys
35 40 45
Ile Arg Asn Ile Gly Ile Ser Ala His Ile Asp Ser Gly Lys Thr
50 55 60
Thr Leu Thr Glu Arg Val Leu Tyr Tyr Thr Gly Arg Ile Ala Lys
65 70 75
Met His Glu Val Lys Gly Lys Asp Gly Val Gly Ala Val Met Asp
80 85 90
Ser Met Glu Leu Glu Arg Gln Arg Gly Ile Thr Ile Gln Ser Ala
95 100 105
Ala Thr Tyr Thr Met Trp Lys Asp Val Asn Ile Asn Ile Ile Asp
110 115 120
Thr Pro Gly His Val Asp Phe Thr Ile Glu Val Glu Arg Ala Leu

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	125		130		135
Arg Val Leu Asp	Gly Ala Val Leu Val	Leu Cys Ala Val Gly	Gly		
	140		145		150
Val Gln Cys Gln	Thr Met Thr Val Asn	Arg Gln Met Lys Arg	Tyr		
	155		160		165
Asn Val Pro Phe	Leu Thr Phe Ile Asn	Lys Leu Asp Arg Met	Gly		
	170		175		180
Ser Asn Pro Ala	Arg Ala Leu Gln Gln	Met Arg Ser Lys Leu	Asn		
	185		190		195
His Asn Ala Ala	Phe Met Gln Ile Pro	Met Gly Leu Glu Gly	Asn		
	200		205		210
Phe Lys Gly Ile	Ile Asp Leu Ile Glu	Glu Arg Ala Ile Tyr	Phe		
	215		220		225
Asp Gly Asp Phe	Gly Gln Ile Val Arg	Tyr Gly Glu Ile Pro	Ala		
	230		235		240
Glu Leu Arg Ala	Ala Ala Thr Asp His	Arg Gln Glu Leu Ile	Glu		
	245		250		255
Cys Val Ala Asn	Ser Asp Glu Gln Leu	Gly Glu Met Phe Leu	Glu		
	260		265		270
Glu Lys Ile Pro	Ser Ile Ser Asp Leu	Lys Leu Ala Ile Arg	Arg		
	275		280		285
Ala Thr Leu Lys	Arg Ser Phe Thr Pro	Val Phe Leu Gly Ser	Ala		
	290		295		300
Leu Lys Asn Lys	Gly Val Gln Pro Leu	Leu Asp Ala Val Leu	Glu		
	305		310		315
Tyr Leu Pro Asn	Pro Ser Glu Val Gln	Asn Tyr Ala Ile Leu	Asn		
	320		325		330
Lys Glu Asp Asp	Ser Lys Glu Lys Thr	Lys Ile Leu Met Asn	Ser		
	335		340		345
Ser Arg Asp Asn	Ser His Pro Phe Val	Gly Leu Ala Phe Lys	Leu		
	350		355		360
Glu Val Gly Arg	Phe Gly Gln Leu Thr	Tyr Val Arg Ser Tyr	Gln		
	365		370		375
Gly Glu Leu Lys	Lys Gly Asp Thr Ile	Tyr Asn Thr Arg Thr	Arg		
	380		385		390
Lys Lys Val Arg	Leu Gln Arg Leu Ala	Arg Met His Ala Asp	Met		
	395		400		405
Met Glu Asp Val	Glu Glu Val Tyr Ala	Gly Asp Ile Cys Ala	Leu		
	410		415		420
Phe Gly Ile Asp	Cys Ala Ser Gly Asp	Thr Phe Thr Asp Lys	Ala		
	425		430		435
Asn Ser Gly Leu	Ser Met Glu Ser Ile	His Val Pro Asp Pro	Val		
	440		445		450
Ile Ser Ile Ala	Met Lys Pro Ser Asn	Lys Asn Asp Leu Glu	Lys		
	455		460		465
Phe Ser Lys Gly	Ile Gly Arg Phe Thr	Arg Glu Asp Pro Thr	Phe		
	470		475		480
Lys Val Tyr Phe	Asp Thr Glu Asn Lys	Glu Thr Val Ile Ser	Gly		
	485		490		495
Met Gly Glu Leu	His Leu Glu Ile Tyr	Ala Gln Arg Leu Glu	Arg		
	500		505		510
Glu Tyr Gly Cys	Pro Cys Ile Thr Gly	Lys Pro Lys Val Ala	Phe		
	515		520		525
Arg Glu Thr Ile	Thr Ala Pro Val Pro	Phe Asp Phe Thr His	Lys		
	530		535		540
Lys Gln Ser Gly	Gly Ala Gly Gln Tyr	Gly Lys Val Ile Gly	Val		
	545		550		555
Leu Glu Pro Leu	Asp Pro Glu Asp Tyr	Thr Lys Leu Glu Phe	Ser		
	560		565		570
Asp Glu Thr Phe	Gly Ser Asn Ile Pro	Lys Gln Phe Val Pro	Ala		
	575		580		585
Val Glu Lys Gly	Phe Leu Asp Ala Cys	Glu Lys Gly Pro Leu	Ser		
	590		595		600

Gly	His	Lys	Leu	Ser	Gly	Leu	Arg	Phe	Val	Leu	Gln	Asp	Gly	Ala	
				605					610						615
His	His	Met	Val	Asp	Ser	Asn	Glu	Ile	Ser	Phe	Ile	Arg	Ala	Gly	
				620					625						630
Glu	Gly	Ala	Leu	Lys	Gln	Ala	Leu	Ala	Asn	Ala	Thr	Leu	Cys	Ile	
				635					640						645
Leu	Glu	Pro	Ile	Met	Ala	Val	Glu	Val	Val	Ala	Pro	Asn	Glu	Phe	
				650					655						660
Gln	Gly	Gln	Val	Ile	Ala	Gly	Ile	Asn	Arg	Arg	His	Gly	Val	Ile	
				665					670						675
Thr	Gly	Gln	Asp	Gly	Val	Glu	Asp	Tyr	Phe	Thr	Leu	Tyr	Ala	Asp	
				680					685						690
Val	Pro	Leu	Asn	Asp	Met	Phe	Gly	Tyr	Ser	Thr	Glu	Leu	Arg	Ser	
				695					700						705
Cys	Thr	Glu	Gly	Lys	Gly	Glu	Tyr	Thr	Met	Glu	Tyr	Ser	Arg	Tyr	
				710					715						720
Gln	Pro	Cys	Leu	Pro	Ser	Thr	Gln	Glu	Asp	Val	Ile	Asn	Lys	Tyr	
				725					730						735
Leu	Glu	Ala	Thr	Gly	Gln	Leu	Pro	Val	Lys	Lys	Gly	Lys	Ala	Lys	
				740					745						750

Asn

&lt;210&gt; 61

&lt;211&gt; 666

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; misc\_feature

&lt;223&gt; Incyte ID No: 3357264CD1

&lt;220&gt;

&lt;221&gt; unsure

&lt;222&gt; 281

&lt;223&gt; unknown or other

&lt;400&gt; 61

Met	Cys	Gly	Ala	Val	Ile	Pro	Leu	His	Lys	Pro	Ala	Gly	Arg	Lys	
				5					10						15
Leu	Gln	Asn	Gln	Arg	Ala	Ala	Leu	Asn	Gln	Gln	Ile	Leu	Lys	Ala	
				20					25						30
Val	Arg	Met	Arg	Thr	Gly	Ala	Glu	Asn	Leu	Leu	Lys	Val	Ala	Thr	
				35					40						45
Asn	Ser	Lys	Val	Arg	Glu	Gln	Val	Arg	Leu	Glu	Leu	Ser	Phe	Val	
				50					55						60
Asn	Ser	Asp	Leu	Gln	Met	Leu	Lys	Glu	Glu	Leu	Glu	Gly	Leu	Asn	
				65					70						75
Ile	Ser	Val	Gly	Val	Tyr	Gln	Asn	Thr	Glu	Glu	Ala	Phe	Thr	Ile	
				80					85						90
Pro	Leu	Ile	Pro	Leu	Gly	Leu	Lys	Glu	Thr	Lys	Asp	Val	Asp	Phe	
				95					100						105
Ala	Val	Val	Leu	Lys	Asp	Phe	Ile	Leu	Glu	His	Tyr	Ser	Glu	Asp	
				110					115						120
Gly	Tyr	Leu	Tyr	Glu	Asp	Glu	Ile	Ala	Asp	Leu	Met	Asp	Leu	Arg	
				125					130						135
Gln	Ala	Cys	Arg	Thr	Pro	Ser	Arg	Asp	Glu	Ala	Gly	Val	Glu	Leu	
				140					145						150
Leu	Met	Thr	Tyr	Phe	Ile	Gln	Leu	Gly	Phe	Val	Glu	Ser	Arg	Phe	
				155					160						165
Phe	Pro	Pro	Thr	Arg	Gln	Met	Gly	Leu	Leu	Phe	Thr	Trp	Tyr	Asp	
				170					175						180
Ser	Leu	Thr	Gly	Val	Pro	Val	Ser	Gln	Gln	Asn	Leu	Leu	Leu	Glu	
				185					190						195

Lys	Ala	Ser	Val	Leu	Phe	Asn	Thr	Gly	Ala	Leu	Tyr	Thr	Gln	Ile
				200					205					210
Gly	Thr	Arg	Cys	Asp	Arg	Gln	Thr	Gln	Ala	Gly	Leu	Glu	Ser	Ala
				215					220					225
Ile	Asp	Ala	Phe	Gln	Arg	Ala	Ala	Gly	Val	Leu	Asn	Tyr	Leu	Lys
				230					235					240
Asp	Thr	Phe	Thr	His	Thr	Pro	Ser	Tyr	Asp	Met	Ser	Pro	Ala	Met
				245					250					255
Leu	Ser	Val	Leu	Val	Lys	Met	Met	Leu	Ala	Gln	Ala	Gln	Glu	Ser
				260					265					270
Val	Phe	Glu	Lys	Ile	Ser	Leu	Pro	Gly	Ile	Xaa	Asn	Glu	Phe	Phe
				275					280					285
Met	Leu	Val	Lys	Val	Ala	Gln	Glu	Ala	Ala	Lys	Val	Gly	Glu	Val
				290					295					300
Tyr	Gln	Gln	Leu	His	Ala	Ala	Met	Ser	Gln	Ala	Pro	Val	Lys	Glu
				305					310					315
Asn	Ile	Pro	Tyr	Ser	Trp	Ala	Ser	Leu	Ala	Cys	Val	Lys	Ala	His
				320					325					330
His	Tyr	Ala	Ala	Leu	Ala	His	Tyr	Phe	Thr	Ala	Ile	Leu	Leu	Ile
				335					340					345
Asp	His	Gln	Val	Lys	Pro	Gly	Thr	Asp	Leu	Asp	His	Gln	Glu	Lys
				350					355					360
Cys	Leu	Ser	Gln	Leu	Tyr	Asp	His	Met	Pro	Glu	Gly	Leu	Thr	Pro
				365					370					375
Leu	Ala	Thr	Leu	Lys	Asn	Asp	Gln	Gln	Arg	Arg	Gln	Leu	Gly	Lys
				380					385					390
Ser	His	Leu	Arg	Arg	Ala	Met	Ala	His	His	Glu	Glu	Ser	Val	Arg
				395					400					405
Glu	Ala	Ser	Leu	Cys	Lys	Lys	Leu	Arg	Thr	Ile	Glu	Val	Leu	Gln
				410					415					420
Lys	Val	Leu	Cys	Ala	Ala	Gln	Glu	Arg	Ser	Arg	Leu	Thr	Tyr	Ala
				425					430					435
Gln	His	Gln	Glu	Glu	Asp	Asp	Leu	Leu	Asn	Leu	Ile	Asp	Ala	Pro
				440					445					450
Ser	Val	Val	Ala	Lys	Thr	Glu	Gln	Glu	Val	Asp	Ile	Ile	Leu	Pro
				455					460					465
Gln	Phe	Ser	Lys	Leu	Thr	Val	Thr	Asp	Phe	Phe	Gln	Lys	Leu	Gly
				470					475					480
Pro	Leu	Ser	Val	Phe	Ser	Ala	Asn	Lys	Arg	Trp	Thr	Pro	Pro	Arg
				485					490					495
Ser	Ile	Arg	Phe	Thr	Ala	Glu	Glu	Gly	Asp	Leu	Gly	Phe	Thr	Leu
				500					505					510
Arg	Gly	Asn	Ala	Pro	Val	Gln	Val	His	Phe	Leu	Asp	Pro	Tyr	Cys
				515					520					525
Ser	Ala	Ser	Val	Ala	Gly	Ala	Arg	Glu	Gly	Asp	Tyr	Ile	Val	Ser
				530					535					540
Ile	Gln	Leu	Val	Asp	Cys	Lys	Trp	Leu	Thr	Leu	Ser	Glu	Val	Met
				545					550					555
Lys	Leu	Leu	Lys	Ser	Phe	Gly	Glu	Asp	Glu	Ile	Glu	Met	Lys	Val
				560					565					570
Val	Ser	Leu	Leu	Asp	Ser	Thr	Ser	Ser	Met	His	Asn	Lys	Ser	Ala
				575					580					585
Thr	Tyr	Ser	Val	Gly	Met	Gln	Lys	Thr	Tyr	Ser	Met	Ile	Cys	Leu
				590					595					600
Ala	Ile	Asp	Asp	Asp	Asp	Lys	Thr	Asp	Lys	Thr	Lys	Lys	Ile	Ser
				605					610					615
Lys	Lys	Leu	Ser	Phe	Leu	Ser	Trp	Gly	Thr	Asn	Lys	Asn	Arg	Gln
				620					625					630
Lys	Ser	Ala	Ser	Thr	Leu	Cys	Leu	Pro	Ser	Val	Gly	Ala	Ala	Arg
				635					640					645
Pro	Gln	Val	Lys	Lys	Lys	Leu	Pro	Ser	Pro	Phe	Ser	Leu	Leu	Asn
				650					655					660
Ser	Asp	Ser	Ser	Trp	Tyr									

665

<210> 62  
 <211> 746  
 <212> PRT  
 <213> Homo sapiens

<220>  
 <221> misc\_feature  
 <223> Incyte ID No: 3576329CD1

<400> 62  
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 Arg Pro Glu Lys Arg Arg Ser Glu Pro Glu Leu Glu Pro Glu Pro  
 20 25 30  
 Glu Pro Glu Pro Pro Leu Leu Cys Thr Ser Pro Leu Ser His Ser  
 35 40 45  
 Thr Gly Ser Asp Ser Gly Val Ser Asp Ser Glu Glu Ser Val Phe  
 50 55 60  
 Ser Gly Leu Glu Asp Ser Gly Ser Asp Ser Ser Glu Asp Asp Asp  
 65 70 75  
 Glu Gly Asp Glu Glu Gly Glu Asp Gly Ala Leu Asp Asp Glu Gly  
 80 85 90  
 His Ser Gly Ile Lys Lys Thr Thr Glu Glu Gln Val Gln Ala Ser  
 95 100 105  
 Thr Pro Cys Pro Arg Thr Glu Met Ala Ser Ala Arg Ile Gly Asp  
 110 115 120  
 Glu Tyr Ala Glu Asp Ser Ser Asp Glu Glu Asp Ile Arg Asn Thr  
 125 130 135  
 Val Gly Asn Val Pro Leu Glu Trp Tyr Asp Asp Phe Pro His Val  
 140 145 150  
 Gly Tyr Asp Leu Asp Gly Arg Arg Ile Tyr Lys Pro Leu Arg Thr  
 155 160 165  
 Arg Asp Glu Leu Asp Gln Phe Leu Asp Lys Met Asp Asp Pro Asp  
 170 175 180  
 Tyr Trp Arg Thr Val Gln Asp Pro Met Thr Gly Arg Asp Leu Arg  
 185 190 195  
 Leu Thr Asp Glu Gln Val Ala Leu Val Arg Arg Leu Gln Ser Gly  
 200 205 210  
 Gln Phe Gly Asp Val Gly Phe Asn Pro Tyr Glu Pro Ala Val Asp  
 215 220 225  
 Phe Phe Ser Gly Asp Val Met Ile His Pro Val Thr Asn Arg Pro  
 230 235 240  
 Ala Asp Lys Arg Ser Phe Ile Pro Ser Leu Val Glu Lys Glu Lys  
 245 250 255  
 Val Ser Arg Met Val His Ala Ile Lys Met Gly Trp Ile Gln Pro  
 260 265 270  
 Arg Arg Pro Arg Asp Pro Thr Pro Ser Phe Tyr Asp Leu Trp Ala  
 275 280 285  
 Gln Glu Asp Pro Asn Ala Val Leu Gly Arg His Lys Met His Val  
 290 295 300  
 Pro Ala Pro Lys Leu Ala Leu Pro Gly His Ala Glu Ser Tyr Asn  
 305 310 315  
 Pro Pro Pro Glu Tyr Leu Leu Ser Glu Glu Glu Arg Leu Ala Trp  
 320 325 330  
 Glu Gln Gln Glu Pro Gly Glu Arg Lys Leu Gly Phe Leu Pro Arg  
 335 340 345  
 Lys Phe Pro Ser Leu Arg Ala Val Pro Ala Tyr Gly Arg Phe Ile  
 350 355 360  
 Gln Glu Arg Phe Glu Arg Cys Leu Asp Leu Tyr Leu Cys Pro Arg  
 365 370 375  
 Gln Arg Lys Met Arg Val Asn Val Asp Pro Glu Asp Leu Ile Pro  
 380 385 390

Lys Leu Pro Arg Pro Arg Asp Leu Gln Pro Phe Pro Thr Cys Gln  
 395 400 405  
 Ala Leu Val Tyr Arg Gly His Ser Asp Leu Val Arg Cys Leu Ser  
 410 415 420  
 Val Ser Pro Gly Gly Gln Trp Leu Val Ser Gly Ser Asp Asp Gly  
 425 430 435  
 Ser Leu Arg Leu Trp Glu Val Ala Thr Ala Arg Cys Val Arg Thr  
 440 445 450  
 Val Pro Val Gly Gly Val Val Lys Ser Val Ala Trp Asn Pro Ser  
 455 460 465  
 Pro Ala Val Cys Leu Val Ala Ala Ala Val Glu Asp Ser Val Leu  
 470 475 480  
 Leu Leu Asn Pro Ala Leu Gly Asp Arg Leu Val Ala Gly Ser Thr  
 485 490 495  
 Asp Gln Leu Leu Ser Ala Phe Val Pro Pro Glu Glu Pro Pro Leu  
 500 505 510  
 Gln Pro Ala Arg Trp Leu Glu Ala Ser Glu Glu Glu Arg Gln Val  
 515 520 525  
 Gly Leu Arg Leu Arg Ile Cys His Gly Lys Pro Val Thr Gln Val  
 530 535 540  
 Thr Trp His Gly Arg Gly Asp Tyr Leu Ala Val Val Leu Ala Thr  
 545 550 555  
 Gln Gly His Thr Gln Val Leu Ile His Gln Leu Ser Arg Arg Arg  
 560 565 570  
 Ser Gln Ser Pro Phe Arg Arg Ser His Gly Gln Val Gln Arg Val  
 575 580 585  
 Ala Phe His Pro Ala Arg Pro Phe Leu Leu Val Ala Ser Gln Arg  
 590 595 600  
 Ser Val Arg Leu Tyr His Leu Leu Arg Gln Glu Leu Thr Lys Lys  
 605 610 615  
 Leu Met Pro Asn Cys Lys Trp Val Ser Ser Leu Ala Val His Pro  
 620 625 630  
 Ala Gly Asp Asn Val Ile Cys Gly Ser Tyr Asp Ser Lys Leu Val  
 635 640 645  
 Trp Phe Asp Leu Asp Leu Ser Thr Lys Pro Tyr Arg Met Leu Arg  
 650 655 660  
 His His Lys Lys Ala Leu Arg Ala Val Ala Phe His Pro Arg Tyr  
 665 670 675  
 Pro Leu Phe Ala Ser Gly Ser Asp Asp Gly Ser Val Ile Val Cys  
 680 685 690  
 His Gly Met Val Tyr Asn Asp Leu Leu Gln Asn Pro Leu Leu Val  
 695 700 705  
 Pro Val Lys Val Leu Lys Gly His Val Leu Thr Arg Asp Leu Gly  
 710 715 720  
 Val Leu Asp Val Ile Phe His Pro Thr Gln Pro Trp Val Phe Ser  
 725 730 735  
 Ser Gly Ala Asp Gly Thr Val Arg Leu Phe Thr  
 740 745

&lt;210&gt; 63

&lt;211&gt; 212

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; misc\_feature

&lt;223&gt; Incyte ID No: 3805550CD1

&lt;400&gt; 63

Met Ala Gly Pro Gly Pro Gly Pro Gly Asp Pro Asp Glu Gln Tyr  
 1 5 10 15  
 Asp Phe Leu Phe Lys Leu Val Leu Val Gly Asp Ala Ser Val Gly  
 20 25 30  
 Lys Thr Cys Val Val Gln Arg Phe Lys Thr Gly Ala Phe Ser Glu

				35					40					45
Arg	Gln	Gly	Ser	Thr	Ile	Gly	Val	Asp	Phe	Thr	Met	Lys	Thr	Leu
				50					55					60
Glu	Ile	Gln	Gly	Lys	Arg	Val	Lys	Leu	Gln	Ile	Trp	Asp	Thr	Ala
				65					70					75
Gly	Gln	Glu	Arg	Phe	Arg	Thr	Ile	Thr	Gln	Ser	Tyr	Tyr	Arg	Ser
				80					85					90
Ala	Asn	Gly	Ala	Ile	Leu	Ala	Tyr	Asp	Ile	Thr	Lys	Arg	Ser	Ser
				95					100					105
Phe	Leu	Ser	Val	Pro	His	Trp	Ile	Glu	Asp	Val	Arg	Lys	Tyr	Ala
				110					115					120
Gly	Ser	Asn	Ile	Val	Gln	Leu	Leu	Ile	Gly	Asn	Lys	Ser	Asp	Leu
				125					130					135
Ser	Glu	Leu	Arg	Glu	Val	Ser	Leu	Ala	Glu	Ala	Gln	Ser	Leu	Ala
				140					145					150
Glu	His	Tyr	Asp	Ile	Leu	Cys	Ala	Ile	Glu	Thr	Ser	Ala	Lys	Asp
				155					160					165
Ser	Ser	Asn	Val	Glu	Glu	Ala	Phe	Leu	Arg	Val	Ala	Thr	Glu	Leu
				170					175					180
Ile	Met	Arg	His	Gly	Gly	Pro	Leu	Phe	Ser	Glu	Lys	Ser	Pro	Asp
				185					190					195
His	Ile	Gln	Leu	Asn	Ser	Lys	Asp	Ile	Gly	Glu	Gly	Trp	Gly	Cys
				200					205					210

Gly Cys

&lt;210&gt; 64

&lt;211&gt; 307

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; misc\_feature

&lt;223&gt; Incyte ID No: 4546403CD1

&lt;400&gt; 64

Met	Arg	Cys	Leu	His	Ser	Glu	Lys	Ala	His	Asp	Leu	Gly	Ile	Thr
1				5					10					15
Cys	Cys	Asp	Phe	Ser	Ser	Gln	Pro	Val	Ser	Asp	Gly	Glu	Gln	Gly
				20					25					30
Leu	Gln	Phe	Phe	Arg	Leu	Ala	Ser	Cys	Gly	Gln	Asp	Cys	Gln	Val
				35					40					45
Lys	Ile	Trp	Ile	Val	Ser	Phe	Thr	His	Ile	Leu	Gly	Phe	Glu	Leu
				50					55					60
Lys	Tyr	Lys	Ser	Thr	Leu	Ser	Gly	His	Cys	Ala	Pro	Val	Leu	Ala
				65					70					75
Cys	Ala	Phe	Ser	His	Asp	Gly	Gln	Met	Leu	Val	Ser	Gly	Ser	Val
				80					85					90
Asp	Lys	Ser	Val	Ile	Val	Tyr	Asp	Thr	Asn	Thr	Glu	Asn	Ile	Leu
				95					100					105
His	Thr	Leu	Thr	Gln	His	Thr	Arg	Tyr	Val	Thr	Thr	Cys	Ala	Phe
				110					115					120
Ala	Pro	Asn	Thr	Leu	Leu	Leu	Ala	Thr	Gly	Ser	Met	Asp	Lys	Thr
				125					130					135
Val	Asn	Ile	Trp	Gln	Phe	Asp	Leu	Glu	Thr	Leu	Cys	Gln	Ala	Arg
				140					145					150
Ser	Thr	Glu	His	Gln	Leu	Lys	Gln	Phe	Thr	Glu	Asp	Trp	Ser	Glu
				155					160					165
Glu	Asp	Val	Ser	Thr	Trp	Leu	Cys	Ala	Gln	Asp	Leu	Lys	Asp	Leu
				170					175					180
Val	Gly	Ile	Phe	Lys	Met	Asn	Asn	Ile	Asp	Gly	Lys	Glu	Leu	Leu
				185					190					195
Asn	Leu	Thr	Lys	Glu	Ser	Leu	Ala	Asp	Asp	Leu	Lys	Ile	Glu	Ser
				200					205					210

Leu Gly Leu Arg Ser Lys Val Leu Arg Lys Ile Glu Glu Leu Arg  
 215 220 225  
 Thr Lys Val Lys Ser Leu Ser Ser Gly Ile Pro Asp Glu Phe Ile  
 230 235 240  
 Cys Pro Ile Thr Arg Glu Leu Met Lys Asp Pro Val Ile Ala Ser  
 245 250 255  
 Asp Gly Tyr Ser Tyr Glu Lys Glu Ala Met Glu Asn Trp Ile Ser  
 260 265 270  
 Lys Lys Lys Arg Thr Ser Pro Met Thr Asn Leu Val Leu Pro Ser  
 275 280 285  
 Ala Val Leu Thr Pro Asn Arg Thr Leu Lys Met Ala Ile Asn Arg  
 290 295 300  
 Trp Leu Glu Thr His Gln Lys  
 305

&lt;210&gt; 65

&lt;211&gt; 378

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; misc\_feature

&lt;223&gt; Incyte ID No: 4767318CD1

&lt;400&gt; 65

Met Arg Ala Ala Ala Ala Pro Gly Leu Thr Ala Pro Trp Arg Leu  
 1 5 10 15  
 Leu Gln Cys Cys Glu Leu Glu Ala Gly Glu Leu Gly Met Ala Val  
 20 25 30  
 Pro Ala Ala Ala Met Gly Pro Ser Ala Leu Gly Gln Ser Gly Pro  
 35 40 45  
 Gly Ser Met Ala Pro Trp Cys Ser Val Ser Ser Gly Pro Ser Arg  
 50 55 60  
 Tyr Val Leu Gly Met Gln Glu Leu Phe Arg Gly His Ser Lys Thr  
 65 70 75  
 Arg Glu Phe Leu Ala His Ser Ala Lys Val His Ser Val Ala Trp  
 80 85 90  
 Ser Cys Asp Gly Arg Arg Leu Ala Ser Gly Ser Phe Asp Lys Thr  
 95 100 105  
 Ala Ser Val Phe Leu Leu Glu Lys Asp Arg Leu Val Lys Glu Asn  
 110 115 120  
 Asn Tyr Arg Gly His Gly Asp Ser Val Asp Gln Leu Cys Trp His  
 125 130 135  
 Pro Ser Asn Pro Asp Leu Phe Val Thr Ala Ser Gly Asp Lys Thr  
 140 145 150  
 Ile Arg Ile Trp Asp Val Arg Thr Thr Lys Cys Ile Ala Thr Val  
 155 160 165  
 Asn Thr Lys Gly Glu Asn Ile Asn Ile Cys Trp Ser Pro Asp Gly  
 170 175 180  
 Gln Thr Ile Ala Val Gly Asn Lys Asp Asp Val Val Thr Phe Ile  
 185 190 195  
 Asp Ala Lys Thr His Arg Ser Lys Ala Glu Glu Gln Phe Lys Phe  
 200 205 210  
 Glu Val Asn Glu Ile Ser Trp Asn Asn Asp Asn Asn Met Phe Phe  
 215 220 225  
 Leu Thr Asn Gly Asn Gly Cys Ile Asn Ile Leu Ser Tyr Pro Glu  
 230 235 240  
 Leu Lys Pro Val Gln Ser Ile Asn Ala His Pro Ser Asn Cys Ile  
 245 250 255  
 Cys Ile Lys Phe Asp Pro Met Gly Lys Tyr Phe Ala Thr Gly Ser  
 260 265 270  
 Ala Asp Ala Leu Val Ser Leu Trp Asp Val Asp Glu Leu Val Cys  
 275 280 285  
 Val Arg Cys Phe Ser Arg Leu Asp Trp Pro Val Arg Thr Leu Ser

	290		295		300
Phe Ser His Asp Gly	Lys Met Leu Ala	Ser Ala Ser Glu Asp	His		
	305		310		315
Phe Ile Asp Ile Ala	Glu Val Glu Thr	Gly Asp Lys Leu Trp	Glu		
	320		325		330
Val Gln Cys Glu Ser	Pro Thr Phe Thr	Val Ala Trp His Pro	Lys		
	335		340		345
Arg Pro Leu Leu Ala	Phe Ala Cys Asp	Asp Lys Asp Gly Lys	Tyr		
	350		355		360
Asp Ser Ser Arg Glu	Ala Gly Thr Val	Lys Leu Phe Gly Leu	Pro		
	365		370		375
Asn Asp Ser					

&lt;210&gt; 66

&lt;211&gt; 466

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; misc\_feature

&lt;223&gt; Incyte ID No: 4834527CD1

&lt;400&gt; 66

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Leu Ser Pro Pro Pro	Thr Glu Pro Thr	Asp Gly Glu Gln Ala	Gly
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Gln Pro Leu Leu Asp	Gly Ala Pro Ser	Ser Ala Ser Leu Glu	Thr
	35	40	45
Leu Ile Gln His Leu	Val Pro Thr Ala	Asp Tyr Tyr Pro Glu	Lys
	50	55	60
Ala Tyr Ile Phe Thr	Phe Leu Leu Ser	Ser Arg Leu Phe Ile	Glu
	65	70	75
Pro Arg Glu Leu Leu	Ala Arg Val Cys	His Leu Cys Ile Glu	Gln
	80	85	90
Gln Gln Leu Asp Lys	Pro Val Leu Asp	Lys Ala Arg Val Arg	Lys
	95	100	105
Phe Gly Pro Lys Leu	Gln Leu Leu Ala	Glu Trp Thr Glu	Thr
	110	115	120
Phe Pro Arg Asp Phe	Gln Glu Glu Ser	Thr Ile Gly His Leu	Lys
	125	130	135
Asp Val Val Gly Arg	Ile Ala Pro Cys	Asp Glu Ala Tyr Arg	Lys
	140	145	150
Arg Met His Gln Leu	Gln Ala Leu His	Gln Lys Leu Ala	Ala
	155	160	165
Leu Arg Gln Gly Pro	Glu Gly Leu Val	Gly Ala Asp Lys Pro	Ile
	170	175	180
Ser Tyr Arg Thr Lys	Pro Pro Ala Ser	Ile His Arg Glu Leu	Leu
	185	190	195
Gly Val Cys Ser Asp	Pro Tyr Thr Leu	Ala Gln Gln Leu Thr	His
	200	205	210
Val Glu Leu Glu Arg	Leu Arg His Ile	Gly Pro Glu Glu Phe	Val
	215	220	225
Gln Ala Phe Val Asn	Lys Asp Pro Leu	Ala Ser Thr Lys Pro	Cys
	230	235	240
Phe Ser Asp Lys Thr	Ser Asn Leu Glu	Ala Tyr Val Lys Trp	Phe
	245	250	255
Asn Arg Leu Cys Tyr	Leu Val Ala Thr	Glu Ile Cys Met Pro	Ala
	260	265	270
Lys Lys Lys Gln Arg	Ala Gln Val Ile	Glu Phe Phe Ile Asp	Val
	275	280	285
Ala Arg Glu Cys Phe	Asn Ile Gly Asn	Phe Asn Ser Leu Met	Ala
	290	295	300



Ile	Ile	Ser	Gly	Met	Asn	Met	Ser	Pro	Val	Ser	Arg	Leu	Lys	Lys	
				305					310					315	
Thr	Trp	Ala	Lys	Val	Arg	Thr	Ala	Lys	Phe	Phe	Ile	Leu	Glu	His	
				320					325					330	
Gln	Met	Asp	Pro	Thr	Gly	Asn	Phe	Cys	Asn	Tyr	Arg	Thr	Ala	Leu	
				335					340					345	
Arg	Gly	Ala	Ala	His	Arg	Ser	Leu	Thr	Ala	His	Ser	Ser	Arg	Glu	
				350					355					360	
Lys	Ile	Val	Ile	Pro	Phe	Phe	Ser	Leu	Leu	Ile	Lys	Asp	Ile	Tyr	
				365					370					375	
Phe	Leu	Asn	Glu	Gly	Cys	Ala	Asn	Arg	Leu	Pro	Asn	Gly	His	Val	
				380					385					390	
Asn	Phe	Glu	Lys	Phe	Leu	Glu	Leu	Ala	Lys	Gln	Val	Gly	Glu	Phe	
				395					400					405	
Ile	Thr	Trp	Lys	Gln	Val	Glu	Cys	Pro	Phe	Glu	Gln	Asp	Ala	Ser	
				410					415					420	
Ile	Thr	His	Tyr	Leu	Tyr	Thr	Ala	Pro	Ile	Phe	Ser	Glu	Asp	Gly	
				425					430					435	
Leu	Tyr	Leu	Ala	Ser	Tyr	Glu	Ser	Glu	Ser	Pro	Glu	Asn	Gln	Thr	
				440					445					450	
Glu	Lys	Glu	Arg	Trp	Lys	Ala	Leu	Arg	Ser	Ser	Ile	Leu	Gly	Lys	
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Thr

&lt;210&gt; 67

&lt;211&gt; 891

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; misc\_feature

&lt;223&gt; Incyte ID No: 1405545CB1

&lt;400&gt; 67

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cagggcggac	aacatcttca	cggccactga	acggaaccgc	atcgactacg	tcagctccgc	300
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caatgttgga	aaatcatctc	taatcaaggc	tttattttca	ctggccccctg	aggttgaagt	420
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&lt;210&gt; 68

&lt;211&gt; 1512

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; misc\_feature

&lt;223&gt; Incyte ID No: 1451265CB1

&lt;400&gt; 68

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aaaaaaaaaa aa 1512

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<210> 69

<211> 2536

<212> DNA

<213> Homo sapiens

<220>

<221> misc\_feature

<223> Incyte ID No: 1556311CB1

<400> 69

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tcttgtctct cgcgacaatt ctctttgaag gcgaggcatt tcaccacaa tcttttcaac 180
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gccttgcaag ggttaccggg ttccggaatt tccccgggg cccctcggct ggccaggact 360
gaaacccaga cgagcatgcc agaaacagtc aaccataaca aacatgggaa cgtagctctc 420
cctggaacga aaccaactcc catccctcca ccccggtga agaagcaggc ttctttctc 480
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&lt;210&gt; 70

&lt;211&gt; 1415

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; misc\_feature

&lt;223&gt; Incyte ID No: 1901373CB1

&lt;400&gt; 70

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gtccctggtc tctccagccc tcaactcgaa ccgcactgac aataccctcc cctcccttgg 180
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tggaaccaag gaagtatgat gctgatgaca acgtgaagat catctgcctg ggagacagcg 300
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&lt;210&gt; 71

&lt;211&gt; 1902

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; misc\_feature

&lt;223&gt; Incyte ID No: 2367767CB1

&lt;400&gt; 71

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&lt;210&gt; 72

&lt;211&gt; 1681

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; misc\_feature

&lt;223&gt; Incyte ID No: 3090433CB1

&lt;400&gt; 72

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<212> DNA
<213> Homo sapiens

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<223> Incyte ID No: 3800591CB1

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<213> Homo sapiens

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<223> Incyte ID No: 5308471CB1

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&lt;210&gt; 75

&lt;211&gt; 2067

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; misc\_feature

&lt;223&gt; Incyte ID No: 5324322CB1

&lt;400&gt; 75

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&lt;210&gt; 76

&lt;211&gt; 2085

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; misc\_feature

&lt;223&gt; Incyte ID No: 067184CB1

&lt;400&gt; 76

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&lt;210&gt; 77

&lt;211&gt; 2061

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; misc\_feature

&lt;223&gt; Incyte ID No: 722896CB1

&lt;400&gt; 77

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&lt;210&gt; 78

&lt;211&gt; 981

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; misc\_feature

&lt;223&gt; Incyte ID No: 1571739CB1

&lt;400&gt; 78

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&lt;210&gt; 79

&lt;211&gt; 1375

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; misc\_feature

&lt;223&gt; Incyte ID No: 1739479CB1



&lt;400&gt; 79

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&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

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&lt;223&gt; Incyte ID No: 1999147CB1

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&lt;223&gt; Incyte ID No: 5519057CB1

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&lt;400&gt; 91

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&lt;400&gt; 93

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&lt;210&gt; 94

&lt;211&gt; 2332

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; misc\_feature

&lt;223&gt; Incyte ID No: 1251632CB1

&lt;400&gt; 94

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&lt;210&gt; 95

&lt;211&gt; 1751

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; misc\_feature

&lt;223&gt; Incyte ID No: 1331955CB1

&lt;400&gt; 95

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&lt;211&gt; 1285

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; misc\_feature

&lt;223&gt; Incyte ID No: 1412614CB1

&lt;400&gt; 96

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<212> DNA

<213> Homo sapiens

<220>

<221> misc\_feature

<223> Incyte ID No: 1750781CB1

<400> 97

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&lt;211&gt; 1276

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; misc\_feature

&lt;223&gt; Incyte ID No: 1821658CB1

&lt;400&gt; 98

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&lt;223&gt; Incyte ID No: 1872574CB1

&lt;400&gt; 99

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&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; misc\_feature

&lt;223&gt; Incyte ID No: 2590967CB1

&lt;400&gt; 100

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&lt;211&gt; 2839

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; misc\_feature

&lt;223&gt; Incyte ID No: 2824491CB1

&lt;400&gt; 101

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&lt;211&gt; 1676

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; misc\_feature

&lt;223&gt; Incyte ID No: 2825460CB1

&lt;400&gt; 102

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&lt;211&gt; 3206

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; misc\_feature

&lt;223&gt; Incyte ID No: 2871116CB1

&lt;400&gt; 103

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&lt;211&gt; 921

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; misc\_feature

&lt;223&gt; Incyte ID No: 2942212CB1

&lt;400&gt; 104

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&lt;211&gt; 1367

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

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&lt;223&gt; Incyte ID No: 3685151CB1

&lt;400&gt; 105

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&lt;223&gt; Incyte ID No: 4881515CB1

&lt;400&gt; 106

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&lt;400&gt; 110

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&lt;213&gt; Homo sapiens

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&lt;223&gt; Incyte ID No: 1751354CB1

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&lt;400&gt; 114

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&lt;223&gt; Incyte ID No: 2048234CB1

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&lt;223&gt; Incyte ID No: 2477507CB1

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&lt;213&gt; Homo sapiens

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&lt;221&gt; misc\_feature

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&lt;223&gt; a, t, c, g, or other

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&lt;210&gt; 123

&lt;211&gt; 2223

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; misc\_feature

&lt;223&gt; Incyte ID No: 3002667CB1

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&lt;220&gt;

&lt;221&gt; misc\_feature

&lt;223&gt; Incyte ID No: 4546403CB1

&lt;400&gt; 130

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&lt;220&gt;

&lt;221&gt; misc\_feature

&lt;223&gt; Incyte ID No: 4767318CB1

&lt;400&gt; 131

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&lt;211&gt; 2136

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; misc\_feature

&lt;223&gt; Incyte ID No: 4834527CB1

&lt;400&gt; 132

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(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization  
International Bureau



(43) International Publication Date  
25 January 2001 (25.01.2001)

PCT

(10) International Publication Number  
**WO 01/05970 A3**

(51) International Patent Classification<sup>7</sup>: C12N 15/12,  
C07K 14/47, G01N 33/53, C12Q 1/68, A61K 38/17,  
C07K 16/18, A01K 67/027

(21) International Application Number: PCT/US00/19698

(22) International Filing Date: 19 July 2000 (19.07.2000)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:  
60/144,595 19 July 1999 (19.07.1999) US  
60/150,460 23 August 1999 (23.08.1999) US  
60/159,849 15 October 1999 (15.10.1999) US

(63) Related by continuation (CON) or continuation-in-part (CIP) to earlier applications:

US 60/144,595 (CIP)  
Filed on 19 July 1999 (19.07.1999)  
US 60/150,460 (CIP)  
Filed on 23 August 1999 (23.08.1999)  
US 60/159,849 (CIP)  
Filed on 15 October 1999 (15.10.1999)

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(81) Designated States (*national*): AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(84) Designated States (*regional*): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published:

— With international search report.

(88) Date of publication of the international search report:  
26 April 2001

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.



WO 01/05970 A3

(54) Title: GTP-BINDING PROTEIN ASSOCIATED FACTORS

(57) Abstract: The invention provides human GTP-binding associated proteins (GBAP) and polynucleotides which identify and encode GBAP. The invention also provides expression vectors, host cells, antibodies, agonists, and antagonists. The invention also provides methods for diagnosing, treating, or preventing disorders associated with expression of GBAP.



# INTERNATIONAL SEARCH REPORT

International Application No  
PCT/US 00/19698

A. CLASSIFICATION OF SUBJECT MATTER  
IPC 7 C12N15/12 C07K14/47 G01N33/53 C12Q1/68 A61K38/17  
C07K16/18 A01K67/027

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)  
IPC 7 C12N C07K G01N C12Q A61K A01K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

STRAND

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>DATABASE EMBEST HUM1 [Online] Entry/Acc.no. AA679577, 4 December 1997 (1997-12-04) HILLIER, L. ET AL.: "zj49c09.s1 Soares fetal liver spleen INFLS S1 Homo sapiens cDNA clone 453616 3' similar to TR:G1230663 G1230663 SIMILAR TO E. COLI HYPOTHETICAL 22.1 KD PROTEIN IN POLA 3' REGION." XP002148938 the whole document</p> <p style="text-align: center;">--- -/--</p>	11-15

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

### \* Special categories of cited documents :

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

- "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- "&" document member of the same patent family

Date of the actual completion of the international search

2 October 2000

Date of mailing of the international search report

08.01.01

Name and mailing address of the ISA

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Smalt, R

## INTERNATIONAL SEARCH REPORT

Inter:      nal Application No

PCT/US 00/19698

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>DATABASE EMBL - EMBEST_HUM13 [Online]  Entry HS1229641, Acc.no. AA429983,  25 May 1997 (1997-05-25)  HILLIER, L. ET AL.: "zw60f01.r1  Soares total fetus Nb2HF8 9w Homo sapiens  cDNA cTone IMAGE:774457 5' similar to  SW:YSXC_BACSU P38424 HYPOTHETICAL 22.0 KD  PROTEIN IN LON-HEMA INTERGENIC REGION ;,  mRNA sequence."  XP002148939  the whole document</p> <p>---</p>	11-15
A	<p>DATABASE EMBL - EMBEST_ROD2 [Online]  Entry/Acc.no. A1122094,  8 September 1998 (1998-09-08)  MARRA, M. ET AL.: "uc46f10.r1 Soares mouse  mammary gland NMLMG Mus musculus cDNA  clone IMAGE:1401067 5' similar to  SW:Y335 MYCGE P47577 HYPOTHETICAL  GTP-BINDING PROTEIN MG335. ;, mRNA  sequence."  XP002148940  the whole document</p> <p>---</p>	
P,X	<p>DATABASE EMBL - EMHUM2 [Online]  Entry/Acc.no. AF161484,  1 February 2000 (2000-02-01)  YE, M. ET AL.: "Homo sapiens HSPC135 mRNA,  complete cds."  XP002148941  the whole document</p> <p>---</p>	1,3,6-9, 11-16, 20,23
P,X	<p>WO 99 58675 A (CHIRON CORP ;HYSEQ INC  (US)) 18 November 1999 (1999-11-18)  the whole document</p> <p>---</p>	11-15
A	<p>CLAPHAM, D.E. ET AL.: "New roles for  G-protein beta-gamma-dimers in  transmembrane signalling."  NATURE,  vol. 365, 30 September 1993 (1993-09-30),  pages 403-6, XP002148967  cited in the application  the whole document</p> <p>-----</p>	

# INTERNATIONAL SEARCH REPORT

International application No.  
PCT/US 00/19698

## Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:  
because they relate to subject matter not required to be searched by this Authority, namely:  
  
Although claims 18, 21 and 24 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☒ Claims Nos.:  
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:  
  
see FURTHER INFORMATION sheet PCT/ISA/210
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

1-28 all partially

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

## FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

Invention 1: Claims 1-28, all partially

A protein with at least 90% identity to seq.ID.1 or biologically active or immunogenic fragment thereof, polynucleotide encoding it, optionally transcriptionally linked to a promoter, cell transformed therewith, transgenic organism comprising said polynucleotide, method for producing said protein using said cell, antibody against said protein, polynucleotides having at least 70% sequence homology to seq.ID.67 of at least 60 nt, method for detecting said nucleic acid by hybridization with a probe of at least 20 nt or by amplification, pharmaceutical composition of the protein, methods for screening for (ant)agonists of the protein or modulators of the proteins expression or activity and compounds identified thereby.

Inventions 2-61: claims 1-28, all partially

Subject matter as defined above under invention 1, but limited to the respective protein/nucleic acid sequences:

2. 2 and 68,
3. 3 and 69,
4. 4 and 70,
5. 5 and 71,
6. 6 and 72,
7. 7 and 73,
8. 8 and 74,
9. 9 and 75,
10. 10 and 76,
11. 11 and 77,
12. 12 and 78,
13. 13 and 79,
14. 14 and 80,
15. 15 and 81,
16. 16 and 82,
17. 17 and 83,
18. 18 and 84,
19. 19 and 85,
20. 20 and 86,
21. 21 and 87,
22. 22 and 88,
23. 24 and 90,
24. 25 and 91,
25. 26 and 92,
26. 27 and 93,
27. 29 and 95,
28. 30 and 96,
29. 31 and 97,
30. 32 and 98,
31. 33 and 99,
32. 34 and 100,

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

33.36 and 102,  
34.37 and 103,  
35.38 and 104,  
36.39 and 105,  
37.40 and 106,  
38.41 and 107,  
39.43 and 109,  
40.44 and 110,  
41.45 and 111,  
42.46 and 112,  
43.47 and 113,  
44.48 and 114,  
45.49 and 115,  
46.50 and 116,  
47.52 and 118,  
48.53 and 119,  
49.54 and 120,  
50.55 and 121,  
51.56 and 122,  
52.57 and 123,  
53.58 and 124,  
54.59 and 125,  
55.60 and 126,  
56.61 and 127,  
57.62 and 128,  
58.63 and 129,  
59.64 and 130,  
60.65 and 131, and  
61.66 and 132.

For the sake of conciseness, the first subject matter is explicitly defined, the other subject matters are defined by analogy thereto.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

## Continuation of Box 1.2

Claim 12 of the underlying application relates to a polynucleotide comprising at least 60 nt of a polynucleotide, which has at least 70% sequence identity to a nucleic acid sequence selected from those listed in claim 5. Since the at least 60 nucleotides need not originate from an area of homology with any of the sequences of claim 5, the polynucleotide claimed in claim 12 is not defined in any way. The search of said claim has been limited to nucleic acids comprising a nucleic acid sequence having at least 70% homology to a nucleic acid sequence selected from claim 5 of at least 60 nt in length.

Present claims 20 and 23 refer to agonists and antagonists, respectively, defined by reference to a desirable characteristic or property, namely the fact that they can be obtained by certain screening methods. The claims cover all compounds having this characteristic or property, whereas the application provides support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT for only a very limited number of such compounds. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Independent of the above reasoning, the claims also lack clarity (Article 6 PCT). An attempt is made to define the compound by reference to a result to be achieved. Again, this lack of clarity in the present case is such as to render a meaningful search over the whole of the claimed scope impossible. Consequently, the search has been carried out for those parts of the claims which appear to be clear, supported and disclosed, namely those parts relating to proteins with at least 90% homology to seq.ID.1 and antibodies thereto.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 00/19698

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